

Top Normal vascular pattern of the liver
Bottom Vascular pattern in severe nutritional cirrhosis

Practical Diagnosis and Treatment of LIVER DISEASE

by
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To

THOMAS J WHITE, M D

AND

ANGELO M GNASSI, M D

WHOSE INSTRUCTION AND ASSISTANCE

MADE THIS VOLUME POSSIBLE

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FOREWORD

This worthwhile treatise on the liver has evolved primarily through clinical observation The author and his associates found themselves confronted by a wide assortment of hepatic disorders and were prompt to organize in their institution a coordinated patient study which is regarded by many as a model of its kind A natural sequence of this painstaking enterprise was an ever-increasing interest in the broader aspects of hepatic physiology and in the pathogenesis of liver disease Their over-all conclusions are presented here in simple concise language No one without a broad, sound background could have attained such clarity with brevity It is difficult indeed to comprehend the countless intricacies of the liver at work It is even more challenging to select from a nebulous mass of factual and mythical teachings the concepts which are of greatest use to others in viewing a difficult subject in perspective

FRANKLIN M HANGER, M D

PREFACE

This monograph is intended to provide a concise, current guide to the practicing physician who is faced with an increasing number of patients with hepatic disease Many of the reported observations were made possible by a coordinated hospital and out-patient program for long-term evaluation of patients with liver disease at the Jersey City Medical Center. The conclusions drawn are based on results of clinical research and experiences in diagnosis and treatment of one thousand consecutive patients hospitalized with various hepatic disorders.

These studies have led to a composite approach to liver disease, based on the ability to determine etiology, clinical status, biochemical functional reserve, and histopathology in vivo Derived data have been used in this presentation to acquaint the reader with the significance and pathophysiologic mechanisms responsible for common clinical features of liver disease, proper choice and value of liver function tests, techniques, indications, complications, and therapeutic value of liver biopsy, and with a specific program for management of common diseases of the liver and their complications.

While the author alone must accept responsibility for the material presented, this book would not have been possible without the aid, support and [illegible]

Earl J Halligan, Felix Traugott, and the members of the attending, resident, and laboratory staffs of the Jersey City Medical

Center who gave so unselfishly of their time in the research program Special thanks are extended to Miss Eileen Quirk for her industry and patience in helping to prepare and edit the manuscript

Expressed opinions have been greatly influenced by an opportunity to study experimental liver injury at the Banting-Best Department of Medical Research, University of Toronto, during the tenure of an A. Blaine Brower Traveling Fellowship of the American College of Physicians The manuscript was completed while the author was serving as a staff officer at the U.S. Naval Hospital, St Albans, Long Island, New York. It reflects concepts developed during this period through clinical conferences, discussions in pathology, and participation in basic investigations which involved radioisotope technics, hepatic vein catheterization, tissue culture experiments, and hormone assays

Although its contents evolved over a period of several years, this monograph only became a reality under the expert guidance of Mr Paul B. Hoeber and his staff After the manuscript was complete, it was decided that its value as an educational medium would be greatly enhanced by reproduction of color photographs available from lectures and scientific exhibits. This was made possible by a grant from Wallace and Tiernan, Inc, Belleville, New Jersey.

C. M L

Practical Diagnosis
and Treatment of
LIVER DISEASE

1

A COMPOSITE APPROACH

THE RELATIVE value of clinical, biochemical, and histologic studies of the liver has been the subject of considerable discussion Many workers suggest clinical appraisal provides the most valuable information, while others emphasize the need for biochemical and anatomic studies Data from 1000 consecutive patients with liver disease receiving a composite of these studies in the Jersey City Medical Center have been reviewed to evaluate the usefulness of individual methods in practice The results indicate that a composite approach with serial evaluation of clinical, biochemical, and histologic status is vastly superior to any specific method of study, and greatly improves diagnostic and therapeutic perspective in the patient with liver disease

The importance of a composite approach in the patient with liver disease is demonstrated by the frequent lack of correlation of available studies Although a complete evaluation of every patient is not needed, the clinician should have a clear concept of what each study, if performed, should show In addition to a knowledge of clinical and laboratory abnormalities which accompany various hepatic disorders, proper use of current study methods is based on an understanding of the physiology, biochemistry, and anatomy of the normal and the diseased liver.

MORPHOLOGIC CONSIDERATIONS

The liver is the largest gland in the body In healthy adults, it weighs 1300–1700 gm and comprises about 3–4% of the total body weight. It is derived from an evagination of the primitive foregut in the form of a compound tubular gland. The adult liver consists of a right and left lobe On the posterior-inferior surface of the right lobe there are two smaller lobes, the caudate and quadrate This organ is attached to the diaphragm and anterior abdominal wall by the falciform, triangular, and coronary ligaments; and to the gastrointestinal tract by the hepatogastric and hepatoduodenal ligaments. It is enveloped by a thin sheath of cellular tissue (Glisson's capsule) which contains blood vessels, lymphatics, and nerve fibers

The parenchymal cell forms the principal unit of the liver. This cell may vary in shape but it is usually polygonal and has six or more surfaces so arranged as to provide maximum exposure to adjacent vascular channels The normal liver cell contains a single vesicular nucleus which has prominent nucleoli and small chromatic dots composed predominantly of nucleoproteins. Cytoplasm consists of mitochondria, microsomes, Golgi bodies, and other structures responsible for cellular work. There is cytoplasmic basophilia (ergastoplasm) due to pentose nucleic acids. Histologic appearance of the cytoplasm depends upon the relative content of fat, glycogen, protein, iron, vitamin A, phosphatase, esterase, and other substances. The activity of the liver cell is determined by the relative proportion of these materials which are organized through metabolic systems entrenched in enzymes and coenzymes (1)

Liver cells are arranged in plates of one cell thickness which surround an irregular labyrinthine cavity (2) Sinusoids occur between the hepatic plates, and are separated from the liver cells by a potential tissue space (space of Dissé) Kupffer cells, which are the reticuloendothelial cells of the liver, are attached to the walls of the sinusoids Bile capillaries are found in grooves between the liver cells. These form a network which empties into

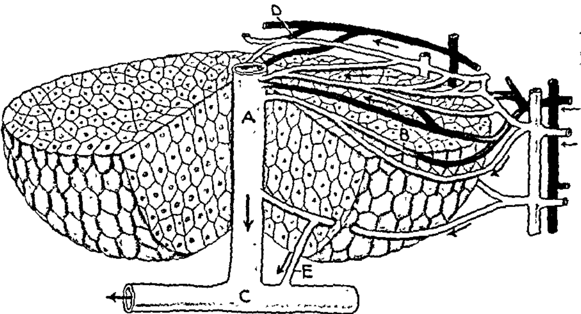


Fig 1 The anatomic lobule of the liver A, central vein, B, portal venule, C, hepatic vein, D, anastomosis between portal vein and hepatic artery, E, branch of hepatic artery.

cholangioles. Parenchymal cells lie between the vascular bed and biliary tract and maintain a constant interchange with these two systems

Aggregates of liver cells form microscopic lobules. The ana-

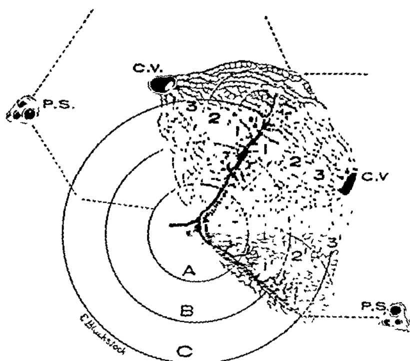


FIG 2. The hepatic acinus (Rappaport) constructed from perfusion experiments. The human liver differs in that the area around the portal triad is also supplied by branches of the portal vein, hepatic artery and bile duct C.V., central vein, P S, portal system The numbers 1, 2, 3, and letters A, B, C, designate areas in relation to the acinus. (Rappaport, Borowy, Lougheed, and Lotto Anat Rec, *119* 11, 1954)

tomic lobule consists of a central vein, liver cells, and the portal triad. The portal triad contains branches of the hepatic artery, portal vein, bile ducts, and lymph channels and is surrounded by the tissue space of Mall (Fig. 1). Functionally, the center of the hepatic lobule is in the area of the *terminal branches* of the portal vein, hepatic artery, and bile duct (3). Here the

major metabolic processes are performed. There is a progressive decrease in oxygen and an increased susceptibility to injury as one gets farther from this area (Fig 2)

Hepatic blood flow in man ranges between 1085 and 1845 ml./minute. The portal vein and hepatic artery bring blood to the liver, the amount supplied by each vessel depending upon functional requirements The liver may be supported by collateral circulation as demonstrated by clinical experiences with ligation of the hepatic artery or portal vein. Normally, two thirds to three fourths of the blood is supplied by the portal vein which carries most of the absorbed food assimilated by the liver The pressure in the portal vein is normally 100–120 mm H_2O Blood from the splenic, gastric, and inferior mesenteric veins is carried principally to the left lobe, and blood from the small bowel and right colon is carried mainly to the right lobe of the liver Digestion, exercise, and increased metabolic activities accelerate portal blood flow The selective distribution of portal blood causes localization of liver abscesses In experimental animals, decreased portal blood flow is accompanied by atrophy, and an increase is associated with hypertrophy of the liver (4)

Most of the blood-borne oxygen is supplied by the hepatic artery, branches of which enter the portal canal and the liver lobule Hepatic artery pressure is approximately 120 mm Hg This vessel supplies 40–60 per cent of the oxygen of the liver although it may contribute only 10–40 per cent of the total blood flow Branches of the hepatic artery and portal vein empty into the sinusoids either together or independently There may be a communication between smaller branches of the portal vein and hepatic artery while each continues its independent course, or they may join to form a common channel. Blood leaves the liver by the hepatic veins which are formed from the central veins, and empty into the inferior vena cava Transillumination studies in man and animals suggest that there is a variation in blood flow in different areas of the lobule Visualized sinusoids may show transition from complete circulatory inactivity to full activity (5).

Intralobular bile capillaries lead to intralobular, interlobular,

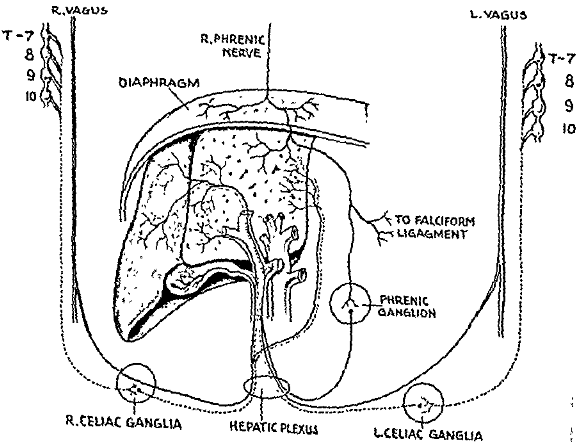


Fig 3. Nerve supply of the liver.

and finally sublobular bile ducts The sublobular ducts empty into the right and left extrahepatic ducts which unite to form the hepatic duct The hepatic duct joins the cystic duct and forms the common bile duct which opens into the duodenum at the ampulla of Vater Normally, the liver secretes 500–1000 ml of bile into the biliary tree over a 24-hour period Bile serves as an excretory vehicle for many substances It consists of bile pigments, bile salts, bile acids, lecithin, cholesterol, inorganic salts, and water Bile formation is increased with an increment in hepatic blood flow, intravenous bile acids, splanchnisectomy, vagal stimulation, ingestion of protein or fats, and administration of choleretics which include secretin, salicylates, cinchophen, pilocarpine, histamine, and acetylcholine

Hydrocholeretics, the most effective of which is dehydrocholic acid (an oxidation product of cholic acid) enhance bile flow by increasing the volume of bile to a greater extent than solids (6).

The nerve supply of the liver consists of the hepatic and phrenic plexuses (Fig 3) There is an anterior hepatic plexus made up of sympathetic postganglionic fibers originating in the left celiac ganglion and preganglionic fibers from T_7 to T_{10} A posterior hepatic plexus consists of postganglionic fibers from the right celiac ganglion and preganglionic fibers from T_7 to T_{10}, joined by preganglionic fibers from the right abdominal branch of the left vagus These nerves ramify through the liver with the hepatic artery and bile ducts The hepatic capsule and the coronary and falciform ligaments have afferent fibers which enter the phrenic plexus (7) Distention of the hepatic capsule, tension on hepatic ligaments, or inflammation of the hepatic parenchyma stimulate pain responses

Lymphatic channels form an extensive network in the hepatic capsule and the portal tracts Lymph vessels appear within the walls of the bile ducts Periportal lymphatics drain toward the hilar area and empty into the thoracic duct It has been estimated that the equivalent of 70-207 per cent of total circulating plasma proteins pass through the lymphatics of the liver in 24 hours Hepatic lymphatics contribute approximately one fourth to one half of the total volume of lymph in the thoracic duct The

protein content of hepatic lymph is five sixths that of blood plasma, sugar and chloride content is higher than that of plasma. Food, exercise, and venous congestion increase lymph flow.

PHYSIOLOGY

The liver is essential for the metabolism of bile, carbohydrates, proteins, and fats, detoxication, storage of metabolites, blood, and water, and manufacture of materials necessary for coagula-

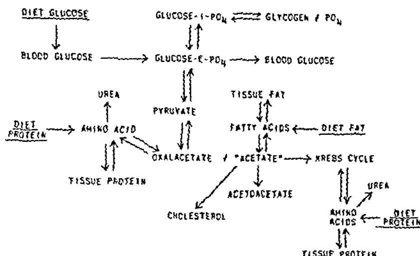


FIG 4 Intermediary metabolism in the liver.

tion and erythropoiesis Bile pigments which represent waste products of hemoglobin and myoglobin are produced by the reticuloendothelial system and carried to the liver where bilirubin is detached from globin (8) Bile salts and bile acids are manufactured by the liver cells and excreted into the biliary passages. They help emulsify fat by lowering surface tension, activate enzymes which digest fat, and make fatty acids water-soluble. This latter action is important for absorption of fat-soluble vitamins. Bile salts also exert an antibacterial effect, and act as choleretics.

The liver is the center of carbohydrate, protein, and fat

metabolism (Fig 4), and is, therefore, the principal site of the release and organization of body energy resources involving phosphorylation and other enzyme systems (1) This organ stores carbohydrate, is the main site of glyconeogenesis from protein and fat, and regulates blood sugar level by processes of synthesis of glycogen and breakdown of glycogen to glucose (9) Albumin, globulins, fibrinogen, and prothrombin are synthesized, nitrogen is stored, deamination and transamination of amino acids carried out, and urea produced from ammonia in the liver (10). Fatty acids are elaborated, oxidized, and phosphorylated, and ketone bodies are formed from fats and protein in this organ It is the site of production and regulation of serum cholesterol which is the precursor of cholic acid, progesterone, and other steroid hormones (11)

Detoxification is a major function of the liver. Substances which are potentially harmful to the body are excreted into the biliary system, destroyed by hepatic parenchymal cells, conjugated with glycuronic acid, amino acids, acetate, sulfate, etc, or temporarily combined with hepatic protoplasm and slowly released The liver serves as a depot for a variety of substances including vitamins B complex, A, D, B_{12}, copper, iron, potassium, manganese, zinc, and cobalt Blood and water are temporarily stored in this organ and slowly released for circulation The liver is the site of production of the prothrombin complex including its precursors and activators, the activators of the thromboplastin complex, and fibrinogen which maintain normal hemostasis It also stores heparin and produces antithrombin and its analogues which help maintain blood fluidity

Symptoms and signs of hepatic disease are related to failure of normal physiologic activities In hepatic insufficiency jaundice is related to abnormal bilirubin metabolism Ease of fatigue, hypoglycemia, or hyperglycemia may result from a disturbance in carbohydrate metabolism Perverted protein metabolism is manifested by hypoalbuminemia, ammonium toxicity, or decreased antibody activity Hypercholesterolemia leads to xanthomatosis, decreased production of hemostatic elements causes bleeding tendencies, and failure to conjugate estrogen results in menstrual

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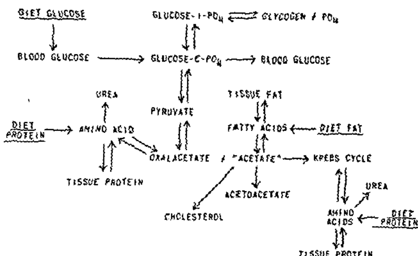


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The liver is the center of carbohydrate, protein, and fat

ultimate pathologic changes When the necrotic process is in the foreground, marked evidence of hepatic insufficiency is present Hepatic fibrosis results from proliferation of connective tissue and/or condensation of reticular stroma, and often leads to slow deterioration of hepatic functional reserve by interfering with the normal blood supply and bile drainage Proliferation of liver cells, bile ducts, and Kupffer cells may prove harmful for they distort normal lobular architecture and occasionally serve as the site of origin of neoplasia

TECHNICS OF A COMPOSITE DIAGNOSIS

When clinical or laboratory findings indicate the presence of liver disease, the physician must first determine its cause (13) The etiology of liver disease is usually established by history and physical examination, but occasionally it is necessary to perform other studies The major contributing cause in the series of 1000 patients with hepatic disorders studied in the Jersey City Medical Center was nutritional deficiency or metabolic errors in 680, infectious and toxic agents in 100, circulatory congestion or anoxia in 120, malignancy in 70, and miscellaneous conditions in 30

Physical examination provides information on liver size, texture, and tenderness It is important to note the presence or absence of jaundice, spider angiomas, hormonal disturbances, splenomegaly, fluid retention, hepatic fetor, and mental changes General laboratory tests should include a chest x-ray, urinalysis, red blood cell count, white blood cell differential, serologic test for syphilis, blood sugar, and blood urea nitrogen Special procedures may be required such as gastrointestinal x-rays, esophagoscopy, hepatic vein catheterization, and bacteriologic, hormonal, hematologic, or electrolyte studies

With gastrointestinal hemorrhage, an esophagram is desirable for the diagnosis of esophageal varices A gastrointestinal series and barium enema are sometimes required to rule out bleeding from concurrent disease Esophagoscopy facilitates detection of esophageal varices and permits estimation of venous pressure through a manometric device introduced into an accessible varix

irregularities, gynecomastia, or testicular atrophy. Disturbance in hepatic regulation of fluid and electrolytes may be responsible for edema, dehydration, or acid-base imbalance

PATHOGENESIS OF LIVER DISEASE

There are four basic causes of liver injury, each of which produces similar clinical, biochemical, and morphologic changes in

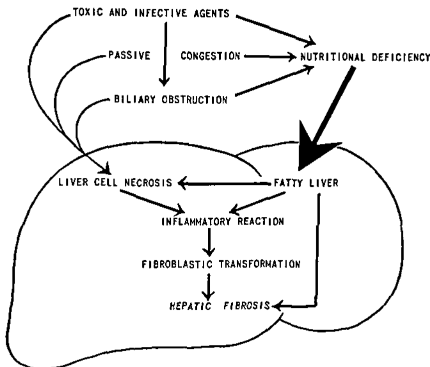


Fig 5 Pathogenesis of liver disease

the end stages (12) Nutritional deficiency and metabolic disturbances, noxious factors, biliary obstruction and infection, and circulatory congestion or anoxia may all eventually lead to death of parenchymal cells, inflammation, increased fibroblastic activity, liver cell regeneration, and bile duct proliferation (Fig 5) The degree of injury and host resistance are the major determinants of

culty. Liver function tests help to differentiate the cause of jaundice, determine the activity of hepatic damage, permit objective following of the course of liver injury, and furnish a basis for treatment. Available tests can be classified into those which measure excretory capacity, those which assay metabolic function, and those which reflect activity of a pathologic process. All tests attempt to quantitate the functional state of integrated enzymatic activity which is influenced by the vigor and mass of hepatic parenchyma, availability of specific metabolites, cellular oxygen supply, and presence or absence of factors that enhance or depress specific enzymes (15).

None of the currently available liver function tests is specific, and each depends upon the functional integrity of extrahepatic tissue. Thus, the bromsulfalein test is abnormal with shock or circulatory congestion, the serum bilirubin may be abnormal due to increased red blood cell destruction in hemolytic disease, the serum alkaline phosphatase is increased with growth and primary diseases of the bone, the total cholesterol is elevated in nephrosis, pregnancy, diabetes, and primary lipid disturbances, and is decreased in starvation, hyperthyroidism, and chronic debilitating diseases, serum glutamic oxaloacetic transaminase is elevated in acute injury of the myocardium, skeletal muscle, brain, or kidney A variety of systemic diseases are accompanied by alteration of plasma protein, the flocculation tests, urine coproporphyrin, choline esterase, and glycogen storage capacity Likewise, cholesterol esterfication, hippuric acid synthesis, and prothrombin production are influenced by nonhepatic processes.

Choice of biochemical tests depends upon the information desired by the clinician. They are of greatest value when performed serially in following the progress of a pathologic process There is frequently no relationship between biochemical and other findings in random studies, however, comparative sequential observations permit good correlation in most patients Evaluation of factors influencing the effectiveness of liver function tests in diagnosis demonstrates the merit of selecting biochemical tests which measure different aspects of functional reserve (16) An attempt has been made to grade severity of biochemical dys-

Catheterization of the hepatic veins to determine the wedged hepatic vein pressure may be helpful in establishing the degree of portal hypertension and assessing the need for surgical therapy for esophageal varices. Cholecystography is valuable when symptoms suggest gallbladder dysfunction, and is useful as a routine procedure in older patients with liver disease because of the high incidence of gallstones and their potential complications.

Bacteriologic and serologic studies are desirable on patients with hepatic disease due to infectious agents. It is important to identify the virus, rickettsia, bacteria, protozoa, or fungus which is responsible for liver injury. This may be done by direct bacteriologic technics or with the aid of complement fixation tests, agglutination studies, or skin tests Use of specific chemotherapy or antibiotics depends upon identification of the etiologic agent Toxicologic study is desirable when a chemical, drug, or heavy metal is thought to be the offending agent in liver cell injury.

Endocrinologic disturbances may be prominent and often necessitate additional laboratory studies Hormonal assays are required for complete evaluation of menstrual abnormalities, impotence, gynecomastia, virilism, or symptoms of adrenal dysfunction. Hematologic investigation is necessary with anemia or bleeding tendency It is essential to determine the cause and type of anemia This requires study of peripheral blood and often involves bone marrow examination, red blood cell survival studies, etc The clotting time, bleeding time, capillary fragility, prothrombin time, prothrombin consumption time, platelet count, and measures of specific substances essential to clotting should be investigated in patients with a bleeding tendency. Proper therapy in edematous patients is facilitated by knowledge of fluid and electrolyte content of the cells as well as interstitial and plasma compartments.

Biochemical liver function tests contribute greatly to diagnosis and treatment if employed as an adjunct to clinical and histologic studies Many different tests have been proposed to measure varying aspects of liver function (14). Tests should be those which can be readily performed and interpreted without diffi-

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CLASSIFICATIONS OF LIVER DISEASE

A composite approach to liver disease permits a classification of hepatic disorders similar to that introduced for heart disease by the American Heart Association (20) A diagnosis based on this principle would include a designation of etiology, clinical state, biochemical functional capacity and anatomy The classification below has been used in the Jersey City Medical Center for serial follow up of patients with liver disease

A ETIOLOGY
 1 NUTRITIONAL DEFICIENCY AND METABOLIC ERRORS
  a Poor dietary intake
   (1) Alcoholism
   (2) Gastrointestinal disease
   (3) Systemic disease
   (4) Food fads
    (a) Inadequate protein intake
    (b) Anorexia nervosa
    (c) Excess caloric intake
  b Abnormal absorption of food
   (1) Pancreatic disease
   (2) Intestinal disease
  c Abnormal assimilation of food
   (1) Diabetes mellitus
   (2) Abnormal thyroid activity
   (3) Obesity (?)
  d Errors of metabolism
   (1) Glycogen storage disease
   (2) Lipoidoses
   (3) Amyloidosis
   (4) Amino aciduria
    (a) Fanconi syndrome
    (b) Hepatolenticular degeneration
   (5) Hemosiderosis
 2 TOXIC AND INFECTIOUS AGENTS
  a Chemicals and drugs
   (1) Carbon tetrachloride
   (2) Chloroform
   (3) Chlortetraethane

function in our studies of the natural history of liver disease. For this purpose, routine excretory tests include bromsulfalein excretion, serum bilirubin, and serum alkaline phosphatase. Metabolic functions are assayed by protein partitions, cholesterol esters, prothrombin time, and glycogen storage Activity of a pathologic process is determined by flocculation tests. Many other tests, including hippuric acid synthesis, urine coproporphyrin, and enzyme studies, provide similar information for long-term investigations.

Needle biopsy of the liver furnishes a method for making an anatomic diagnosis in vivo. This technic, first used in 1895 (17), was largely limited to clinical research until recently. It permits recognition of characteristic hepatic lesions in a variety of systemic diseases, facilitates the differential diagnosis of jaundice; makes a specific anatomic diagnosis in vivo in patients with chronic liver disease, hepatic metastases, and hepatomegaly of uncertain origin, and allows evaluation of the effect of therapy on histology It is a safe, easily performed procedure when the correct technic and precautions are employed. More than 2000 biopsies have been performed in the Jersey City Medical Center with only 1 fatality This death occurred in a patient with a prolonged bleeding time (18). The chief limitation of needle biopsy is the small size of the specimen Correlation of clinical and biochemical data with histologic findings partly compensates for this deficiency

Histologic study is important in determining the degree as well as the type of morphologic alteration. The stage of liver injury, as determined by anatomic study, affords the clinician added insight. This is illustrated by studies of the liver in congestive heart failure. Clinical and biochemical evaluation often fail to provide information on the relationship of hepatic abnormalities to refractoriness to cardiac therapy. Histologic study differentiates passive congestion from hepatic fibrosis, and allows an evaluation of the degree and activity of a fibrotic process. This is important since prognosis in patients with passive congestion and centrilobular fibrosis is related to ability to control cardiac dysfunction, whereas the outlook with diffuse fibrosis usually depends on the hepatic status (19).

3 CIRCULATORY DISTURBANCES
 a Passive congestion
 (1) Chronic circulatory congestion
 (2) Shock
 (3) Hemolytic anemia
 (4) Sickle cell anemia
 (5) Polycythemia
 b Hepatic vessel occlusion
 (1) Ligation
 (2) Thrombosis
 (3) Embolism
 c. Diffuse vascular disease
 (1) Thrombotic thrombopenia
 (2) Periarteritis nodosa
 (3) Rickettsial disease
 d Extramedullary hemopoiesis
 (1) Erythroblastosis foetalis
 (2) Myeloid metaplasia
4 BILIARY OBSTRUCTION
 a Extrahepatic
 (1) Calculus
 (2) Stricture
 (3) Atresia
 (4) Neoplasm
 (a) Biliary epithelium
 (b) Lymphoma
 (c) Pancreatic
 (d) Metastatic
 b Intrahepatic
 (1) Hepatoma
 (2) Cholangioma
 (3) Metastatic neoplasm
 (4) Calculi
5 NEOPLASTIC DISEASES
 a. Primary
 (1) Benign
 (2) Malignant
 (a) Hemangioma
 (b) Adenoma
 (c) Fibroma

- (4) Phosphorus
- (5) Methyl testosterone
- (6) Cinchophen
- (7) Chlorpromazine
- (8) Thiouracil
- (9) Others

b Heavy metals
- (1) Arsenic
- (2) Gold
- (3) Beryllium

c Primary liver infections
- (1) Viral hepatitis
- (2) Yellow fever
- (3) Leptospirosis
- (4) Echinococcosis
- (5) Clonorchiasis

d Secondary liver infections
- (1) Viral infections
  - (a) Infectious mononucleosis
  - (b) Vaccinia
- (2) Bacterial infections
  - (a) Tuberculosis
  - (b) Brucellosis
  - (c) Typhoid
  - (d) Bartonellosis
  - (e) Others
- (3) Spirochaetal infections
  - (a) Syphilis
- (4) Fungus infections
  - (a) Histoplasmosis
  - (b) Toxoplasmosis
  - (c) Coccidioidomycosis
  - (d) Others
- (5) Parasitic infections
  - (a) Malaria
  - (b) Leishmaniasis
  - (c) Schistosomiasis
  - (d) Amoebiasis
  - (e) Others

accompanied by elevation of serum bilirubin and total serum cholesterol

- d Evidence of complete interruption of bile outflow characterized by absent fecal and urine urobilinogen and elevation of serum alkaline phosphatase

2 METABOLIC FUNCTIONAL IMPAIRMENT (graded according to severity)

- a. Abnormality of a sensitive test which reflects parenchymal cell injury as flocculation tests, glycogen storage test, urinary coproporphyrin, or serum glutamic oxalacetate transaminase
- b. Abnormality of less sensitive test which reflects parenchymal cell injury as hippuric acid synthesis and serum cholesterol esters
- c Derangements of albumin or prothrombin synthesis, or abnormality in galactose tolerance
- d Abnormality of blood sugar control, disturbance in conjugation of ammonia and glutamic acid, decrease of serum choline esterase, derangement in synthesis of fibrinogen

D. ANATOMIC STATUS (HISTOPATHOLOGY)

1. FAT (graded according to severity)
   - a Not significant—fat globules occupying less than 10 per cent of the biopsy specimen
   - b Mild fat—fat globules occupying 10–30 per cent of the biopsy specimen
   - c Moderate fat—fat globules occupying 30–80 per cent of the biopsy specimen
   - d Severe fat—fat globules occupying over 80 per cent of the biopsy specimen

2 [illegible]

…en fibers occupy up to 10 per cent of the biopsy specimen

- c Moderate fibrosis—connective tissue elements occupy 10–30 per cent of the biopsy specimen Vascularization of connective tissue with evidence of dissociation of parenchymal cells from vascular and biliary systems
- d Severe fibrosis—connective tissue elements occupy over 30 per cent of the biopsy specimen Parenchymal cells virtually isolated by fibrosis.

b Neoplasms involving reticuloendothelial system
(1) Hodgkin's disease
(2) Lymphosarcoma
(3) Multiple myeloma
(4) Myeloid leukemia
(5) Lymphatic leukemia
(6) Monocytic leukemia

6 TRAUMA TO LIVER
a. Penetrating wounds
b. Traumatic rupture
c Hemobilia

B. CLINICAL STATUS

GRADE 1 SUBCLINICAL LIVER ABNORMALITIES
a. Biochemical alterations without *signs or symptoms* of liver disease
b Histologic alterations without signs or symptoms of liver disease
c. Biochemical and histologic alterations without signs or symptoms of liver disease

GRADE 2 COMPENSATED LIVER DISEASE
a Hepatomegaly and/or hepatic tenderness as the only sign of liver disease
b Hepatomegaly and/or hepatic tenderness plus spider *angiomas*
c Hepatomegaly and/or hepatic tenderness plus splenomegaly.

GRADE 3. LIVER DISEASE WITH DECOMPENSATION
a Jaundice
b. Hepatic fetor
c. Fluid retention
d Bleeding esophageal varices

GRADE 4 TERMINAL LIVER DISEASE
a Hepatic coma

C. BIOCHEMICAL STUDIES

1. EXCRETORY DYSFUNCTION (graded according to severity)
a. Bromsulfalein retention alone.
b Moderate disturbance in bile metabolism reflected in elevation of serum bilirubin, normal alkaline phosphatase
c. Disturbance in excretion of serum alkaline phosphatase,

(3) Puddling of red cells in sinusoids
(4) Hemorrhagic infarction
c Ischemia
(1) Localized
(2) Generalized
d Vascular occlusion
(1) Hepatic artery
(2) Hepatic vein
(3) Portal vein
(4) Multiple vessel involvement.
(a) Periarteritis nodosa
(b) Thrombotic thrombopenia
(c) Rickettsial diseases
8 Extrinsic alterations
a Neoplastic
(1) Primary
(a) Benign
1 Fibroma
2 Adenoma
3 Hemangioma
4 Cysts
(b) Malignant
1 Primary liver cell carcinoma
2 Bile duct carcinoma
(2) Metastatic carcinoma—gastrointestinal tract, lung, breast, kidney, etc
(3) Involvement of reticuloendothelial system—Hodgkin's disease, leukemia, lymphosarcoma
b Infiltrations
(1) Hemosiderin
(2) Lipoidoses
(3) Glycogen
(4) Amyloid

USE OF A COMPOSITE APPROACH IN TREATMENT

Treatment of liver disease should consist of a program designed to control etiologic factors and improve clinical, biochemical, and histologic abnormalities This type of approach provides specific therapeutic orientation and makes it possible to better

3 REGENERATION
  a Liver cell
    (1) Occasional mitoses with maintenance of unicellular cord arrangement.
    (2) Nodular regeneration of liver parenchyma with formation of cords of 2–3 cell layers.
  b Bile duct
    (1) Occasional multiplication of bile ducts in the portal area
    (2) Marked proliferation of bile ducts extending into periportal areas.
  c. Kupffer cell
    (1) Slight increase in number of Kupffer cells.
    (2) Marked increase in number of Kupffer cells.
4 BILE STASIS
  a Bile stasis involving the cholangioles
  b Bile stasis involving large bile channels
  c Bile thrombi
  d. Bile puddling and infarction
5. INFLAMMATION
  a. Localized (focal) inflammation involving perivascular, pericholangiolar, central, or portal area
  b. Diffuse inflammation—inflammatory cells throughout the lobule.
  c Granulomatous process—chronic inflammation with lymphocytic and giant cell reaction
  d. Abcess formation—local collection of pus with an exudate.
6 NECROSIS
  a. Zonal necrosis—localized to one area of hepatic lobule
    (1) Simple
    (2) Hyaline necrosis or acidophilic coagulative necrosis
    (3) Caseation necrosis
  b Autolytic necrosis
7. VASCULAR CHANGES
  a. [illegible]
    [illegible] Dissé)
    [illegible]
  b *Passive congestion*
    (1) Localized
    (2) Generalized

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estimate the prognosis. Serial study permits an over-all evaluation of the influence of treatment, and allows an objective assay of the effectiveness of various therapeutic procedures.

The results of biochemical liver function tests and other laboratory studies aid the physician in his choice of therapy. Thus, in a patient with bleeding esophageal varices, biochemical and histologic evaluation furnishes information as to: (a) the causative mechanism, (b) the potential reversibility of the varices with medical therapy, and (c) the capacity to tolerate surgical therapy. Flocculation tests and bromsulfalein excretion indicate the *activity of parenchymal disease and the need for continued therapy*. Serum albumin, glycogen storage, and serum ammonium facilitate therapeutic orientation in patients with chronic liver disease who exhibit fluid accumulation, generalized weakness and sensorial changes. In selected cases, radiologic examination, bacteriologic studies, or hematologic evaluation provide helpful information.

Histologic study facilitates interpretation of clinical and biochemical findings and furnishes another baseline for evaluation of therapy. Knowledge of the status of the parenchymal cells and the connective tissue stroma in chronic liver disease improves prognostic perspective by providing insight as to the reversibility of anatomic alterations.

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2

CLINICAL DIAGNOSIS

LIVER disease should be suspected whenever there is a history of jaundice, dietary imbalance, alcoholism, exposure to hepatotoxins, or the presence of diseases which commonly cause hepatocellular injury. Fatty liver and nutritional cirrhosis are found in patients with poor dietary habits due to the unavailability of proper food, alcoholism, drug addiction, or systemic disease. Liver disease is frequent in patients with carbon tetrachloride, arsenic, phosphorus, beryllium, and other chemical intoxication, and is an integral part of many viral, bacterial, fungal, and parasitic infections. Hepatic abnormalities are demonstrable in most patients with heart failure, biliary obstruction, and metastatic neoplastic disease.

A thorough medical history is important in studies of liver disease. Viral hepatitis is suggested with the onset of malaise and icterus six weeks after receipt of plasma or other blood products. Nutritional cirrhosis is present in most chronic alcoholic patients with poor food habits who develop jaundice, ascites, and hematemesis. Hemobilia should be suspected when abdominal trauma is followed by recurrent jaundice, melana, pain in the right upper quadrant, and signs and symptoms of peripheral vascular collapse. Liver abscesses is the most probable cause for cough, chills, fever, and right chest and scapular pain in the patient with amoebic dysentery.

Suggestive signs of liver disease include changes in liver size or texture, tenderness, or pain over the hepatic area, jaundice, spider angiomas, hepatic fetor, bleeding esophageal varices, splenomegaly, and ascites Laboratory studies are often required to properly assess signs and symptoms

PHYSICAL EXAMINATION

Liver Size

An accurate estimate of liver size is important to perform aspiration liver biopsy and establish a baseline for subsequent study Physical examination is the best method for evaluating the size of the liver The examiner should be seated and the patient supine, with head extended and legs drawn up The surface area occupied by the liver is determined by percussion The upper border is normally at the level of the fifth intercostal space in the midclavicular line, and the lower border extends to the edge of the right thoracic cage Displacement, atrophy, or enlargement of the liver is determined by alterations in percussion findings.

The lower edge of the liver should be palpated whenever possible Obesity, ascites, and muscular abdominal walls interfere with palpation. Palpation is facilitated by using the finger tips and making movements from the wrist When the liver edge is below the thoracic cage, its extent should be recorded in centimeters Enlargement of the right lobe is measured from the lowest costal cartilage in the midclavicular line Left lobe enlargement is measured from the ensiform cartilage in the midsternal line, and from the thoracic cage in the left midclavicular line

X-ray studies for liver size are helpful as a supplement to physical examination. The liver is best visualized if air is injected into the colon and the stomach distended with air (1). Routine abdominal roentgenograms demonstrate liver enlargement, chest x-rays show an elevated right diaphragm with upward enlargement of the liver from an abscess or neoplastic infiltration (Fig 6) Special radiologic technics permit a reliable estimate of liver size Gastrointestinal x-rays, cholecystography, cholangiography,

2

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or pyelography indirectly establish the presence of liver enlargement.

Hepatomegaly is the most frequently encountered clinical sign of liver disease. An increase in the size of the liver is sometimes difficult to detect for it might not be felt, also, sometimes a palpable liver may be of normal size A liver which is palpable but not enlarged is displaced as a result of change in thoracico-abdominal relationships.

Liver enlargement is due to fatty changes, inflammation, bile stasis, congestion, fibrosis, regenerated liver cells, or infiltration of foreign materials. We have observed 30 patients with an enlarged liver without detectable histologic abnormalities Hepatomegaly regresses when reversible processes respond to treatment, it persists when it is due to regenerated liver lobules or mature fibrous connective tissue

The liver is frequently smaller than normal in the late phase of cirrhosis and in fulminant hepatitis Rapid reduction in liver size is a grave prognostic sign and is often accompanied by early death Atrophy is occasionally selective and may primarily involve but a single lobe of the liver (2)

Liver Texture

Palpation of the liver permits the clinician to tell whether the surface of this organ is smooth or nodular, and to distinguish whether it is soft, firm, or hard Nodules are due to liver cell regeneration, neoplastic disease, or other infiltrative processes Clinical data sometimes permits a diagnosis as to the cause of the nodules, however, biopsy is desirable for accurate diagnosis. The liver is normally soft but becomes firm or hard as a result of pathologic changes Fatty infiltration, bile stasis, and passive congestion produce firm livers Fibrosis, regeneration of liver cells, and bile duct proliferation also cause hardening of the liver. In the end stages of cirrhosis, the liver has a rock-like consistency on palpation The most marked degree of hardening of the liver occurs in patients with metastatic neoplastic infiltration, or primary liver cancer.



FIG 6 Gastrointestinal x-ray demonstrating elevation of the right diaphragm and distortion of the duodenum due to hepatic enlargement from amoebic abscess of the liver.

tenderness, muscle guarding, and ileus. Pelvic examination with cervical and urethral smears and cultures establishes the diagnosis. At operation, there is a localized peritonitis with fibrin over the anterior surface of the liver

Extravasation of blood or introduction of air beneath the hepatic capsule is responsible for the hepatic tenderness and pain seen after completion of a needle biopsy of the liver Pain is sometimes referred to the region of the liver in disease of the diaphragm, gallbladder, pleura, or heart Patients with acute cholecystitis, diaphragmatic pleurisy, pleurodynia, pneumonia, or coronary insufficiency are suspected of having liver disease when there is localized pain in the right upper quadrant of the abdomen.

PHYSICAL SIGNS OF LIVER DISEASE

Jaundice

Jaundice is often the presenting sign of liver disease. It reflects an increase in circulating bilirubin or bilirubin-globin Blood serum is cleared of bilirubin as long as sufficient normal functioning hepatic tissue is present Jaundice is detected by inspection when the serum bilirubin reaches 2 0 mg /100 cc It is readily recognized by inspecting the sclera in daylight. This is the most reliable site

Jaundice in hepatic disease is due to primary liver cell dysfunction, biliary obstruction, and/or hemolysis Liver cell necrosis is the underlying cause for icterus in hepatitis, heart failure, and *nutritional cirrhosis Intrahepatic obstruction of small bile capil*laries due to cholangiolar injury is also responsible for bilirubin accumulation This mechanism is characteristic of viral and toxic hepatitis (see Chapter 8), but may occur in other types of liver disease One fourth of the patients with primary liver disease who develop jaundice have some evidence of biliary obstruction by laboratory tests Histologic study may show inflammatory changes in the portal area or the connective tissue stroma which encircles small bile ducts Rarely, fat, amyloid, or neoplastic infiltration causes mechanical obstruction to bile outflow. In several instances in our clinic, marked jaundice has accompanied fatty liver, and

Hepatic Tenderness and Pain

Tenderness of the liver is a common finding and often provides the first diagnostic clue to hepatic disease. Pain is usually mild; occasionally it is severe and simulates an acute surgical abdomen. It results from stretching of the hepatic capsule, traction on the coronary and falciform ligaments, inflammation of the hepatic parenchyma, or perihepatitis (3) The afferent pathways for this pain are in the hepatic and phrenic plexuses (Fig. 3).

Gradual increase in liver size does not cause pain, although it does produce the sensation of abdominal heaviness. Rapid enlargement of the liver is accompanied by tenderness and occasionally by severe pain Diagnostic difficulty is encountered when tenderness or pain is not accompanied by liver enlargement, jaundice, or other clinical changes. Viral hepatitis without jaundice is notably confusing in this respect Surgical exploration is often undertaken because of the degree and character of pain in patients with fatty liver, viral hepatitis, amoebic abscess, metastatic carcinoma, and acute hepatic congestion

In our experience fatty liver has most frequently simulated a surgical abdomen. Symptoms have been attributed to distention of the hepatic capsule and or rupture of extracellular fatty cysts with resulting inflammation of the parenchyma Most of our patients were alcoholics, and porphyria, acute pancreatitis, and gastritis were considered in the differential diagnosis. Viral hepatitis has been the second most common cause. Two patients with postnecrotic scarring and chronic active hepatitis had recurrent severe abdominal pain necessitating surgical exploration. The mechanism responsible for abdominal pain is obscure in these instances, although it appears to be related to parenchymal inflammation Rapid distention of the hepatic capsule and traction on hepatic ligaments appeared to produce symptoms of an acute abdomen in patients with liver abscess, metastatic carcinoma, and passive congestion.

Gonococcal perihepatitis complicating a salpingitis is associated with *severe pain* in the right upper quadrant which is referred to the shoulder region. Physical findings include fever, abdominal

gm protein, 100 gm fat, 2 gm each of choline and methionine three times daily, and multivitamins Clinical, biochemical, and histologic abnormalities disappeared on this regimen A gallbladder series performed after icterus had receded was normal

Comment This case history demonstrates the ability of intracellular hepatic disease to produce mechanical obstruction to bile outflow and to simulate extrahepatic biliary obstruction.

Hemolysis causes jaundice in patients with liver disease who receive banked blood in which a large number of the red cells are no longer viable Less commonly, hemolytic reactions are due to isohemolysins.

The degree of jaundice is not correlated with the severity of liver disease. Thus it provides little help in evaluating prognosis Many patients with a reversible lesion of the liver such as viral hepatitis or fatty liver have marked icterus When bile salts accumulate in the skin, jaundice is accompanied by pruritus Sometimes itching precedes clinical icterus and permits the clinician to anticipate elevation of the serum bilirubin Pruritus is more common and of greater intensity in patients with jaundice due to biliary obstruction However, this is not a significant symptom in determining the cause of jaundice

Jaundice due to hepatic disease must be differentiated from that caused by hemolytic disease and extrahepatic obstruction Likewise, it must be distinguished from constitutional hyperbilirubinemia Constitutional hyperbilirubinemia or "familial nonhemolytic jaundice" has been used to designate slight or latent jaundice found in a familial disease of unknown origin (4) In some instances, pigment is present in the liver cells of these individuals, in the usual case, however, needle biopsy shows no abnormalities It has been suggested that pigmented liver cells comprise a distinct clinicopathologic entity (5), since most patients with this finding have abnormal liver function tests, demonstrate no response to cholecystography, and exhibit an enlarged, tender liver at some time during the course of their disease We have observed one patient with constitutional hyperbilirubinemia who had liver cell pigmentation, good visualization of the gallbladder, and a lack of any physical evidence of liver disease

subsequent events suggested icterus was due to compression of small bile ducts by extracellular fat.

Case 1 Marked Fatty Liver with Jaundice Simulating Extrahepatic Biliary Obstruction

Clinical Features. M.H., a 54-year-old laborer, was hospitalized because of anorexia associated with weakness and jaundice. There was a history of eating poorly due to consumption of one to two pints of whiskey each day for several years. Physical examination revealed icterus and liver enlargement 6 cm. below the costal cage; there was no splenomegaly, spider angiomas, hepatic fetor, collateral circulation, or fluid retention.

A diagnosis of extrahepatic biliary obstruction was made but surgical intervention was delayed because of findings on liver biopsy. The patient was treated with bed rest, a diet of 350 gm. of carbohydrate, 150

Biochemical study	*Before Therapy*	*After two months of therapy*
Serum bilirubin (mg %)	31.0	0.1
Urine bile	4+	0
Urine urobilinogen	0	1:20
Bromsulfalein (%)		0
Serum alkaline phosphatase (B.U.)	15	3
Total serum cholesterol (mg %)	567	415
Cholesterol esters (mg %)	65	274
Serum albumin (Gm %)	2.3	2.8
Serum globulin (Gm %)	3.3	3.9
Cephalin flocculation	2+	0
Thymol turbidity (units)	2.0	2.0
Glycogen storage rise in blood sugar (mg %)	12	40

Histologic study	*Before therapy*	*After two months of therapy*
Fibrosis	0	0
Fat	4+	0
Regeneration	1+	1+
Bile stasis	2+	0
Infiltration	2+	1+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	Fatty liver with bile stasis	Normal liver

glass or upon palpation. Pressure interferes with the filling of these vessels.

appearance (6). Histologically, they represent either (a) a direct arteriovenous anastomosis, or (b) an overgrown end artery with branching arterioles and capillaries

Spider angiomas are rare in carcinoma metastases of the liver, the early phases of obstructive jaundice, and hepatic congestion in heart failure. They frequently diminish in size and disappear with the subsidence of viral hepatitis, or upon the improvement of hepatic function in nutritional cirrhosis They also occur congenitally and are seen in pregnancy, rheumatic disease, and endocrine disorders

Hepatic Fetor (Liver Breath)

A sweetish, musty odor resembling that of decayed fruit is often noted on the breath of patients with hepatic insufficiency Occasionally, it is prominent enough to fill an entire room. The odor occurs predominantly in patients with severe hepatic fibrosis, and is often present in fulminant viral hepatitis It is usually noted when hepatic coma supervenes in the terminal phases of liver disease Fetor is rarely present in patients with fatty liver, chronic passive congestion, or neoplastic infiltration of the liver This odor is not specific and is observed in the absence of liver disease We have noted it in patients with heart failure receiving thiomercaptans as diuretic agents Concentrated urine from patients with fetor contains a material which has a similar smell and has chemical and physical properties of a tertiary amine (7) Methyl mercaptan has been isolated from the urine in such cases, and this coupled with a high plasma level of methionine suggests that the mercaptan arises by hydrolytic or reductive fission of the sulphur-carbon bond in methionine (8)

The presence and intensity of fetor hepaticus indicates the gravity of the liver disease Survival rates are inversely propor-

Recognition of this disease is important to prevent unnecessary surgical procedures. It usually occurs in young people, produces intermittent jaundice, and is aggravated by intercurrent disease.

The symptom complex and physical signs permit a correct decision as to the cause of jaundice in 75 per cent of patients. Biochemical liver function tests and needle biopsy of the liver increase diagnostic accuracy to 95 per cent. Laboratory studies are particularly important in patients with two mechanisms contributing to icterus.

Xanthomatosis and Skin Pigmentation

Xanthomas or lipid deposits in the skin occur with persistent hyperlipemia due to biliary obstruction. They are often seen in patients with chronic jaundice in both extrahepatic biliary obstruction and primary cholangiolar disease. In xanthoma planum yellowish, slightly raised papules are found most often over the flexor areas of joints and on the eyelids. In xanthoma tuberosum the papules are larger and may grow to the size of a lemon. They are found over extensor surfaces. Xanthomas may decrease in size or disappear with relief of obstruction and reduction of hypercholesterolemia.

Increased skin pigmentation is noted in patients with prolonged jaundice, hemochromatosis, and certain neoplasms which involve the liver. Rarely, nutritional liver disease causes darkening of the skin. Increased skin melanin and hemosiderin are responsible for color changes. Pigmentary change must be differentiated from that seen in adrenal insufficiency, drug intoxication, and other nonhepatic conditions.

Spider Angiomas

Spider angiomas, prominent skin capillaries, and telangiectasis are commonly observed in *liver disease. They sometimes provide* a clue in diagnosis. Spider angiomas are usually located around the face, neck, shoulders, and upper extremities. They consist of a central elevated erythematous body 0.5–1.5 mm. in diameter from which radiate dilated vascular branches giving the appearance of a spider. Pulsations are discernible under a magnifying

glass or upon palpation Pressure interferes with the filling of these vessels.

that abnormal steroid metabolism may be responsible for their appearance (6) Histologically, they represent either (a) a direct arteriovenous anastomosis, or (b) an overgrown end artery with branching arterioles and capillaries

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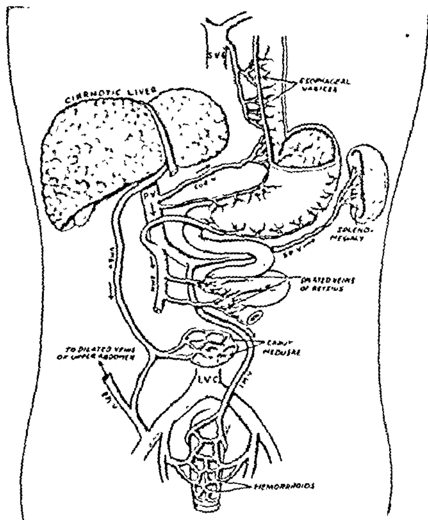


Fig 7 Collateral circulation with portal obstruction

tional to the intensity of the odor. Death often occurs within three to six months after this sign is noted. However, several patients with diffuse hepatic fibrosis have been followed for a period of five years after detecting a liver breath. Liver fetor disappears with improvement of general hepatic reserve.

Collateral Portal Circulation

Collateral circulation develops in patients with intrahepatic abnormalities which interfere with blood flow through the liver Collaterals develop in the abdominal, esophageal, hemorrhoidal,

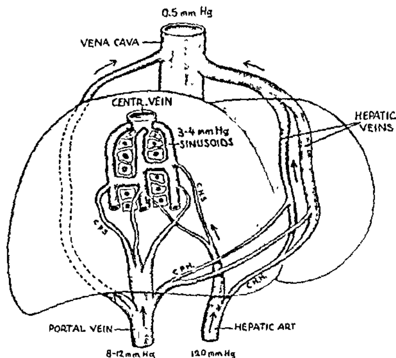


FIG 8 Normal blood supply of the liver showing pressure relationships C P S., collaterals between portal vein and sinusoids, C H S, collaterals between hepatic artery and sinusoids, C P H, collaterals between portal and hepatic veins, C H H, collaterals between hepatic artery and hepatic veins

and retroperitoneal areas to facilitate the return of blood to the heart (Fig 7). Clinical detection of the common collaterals is possible by inspection and auscultation over the upper abdomen, *esophagram or esophagoscopy, and anoscopy or proctoscopy*

Blood normally reaches the liver by way of the portal vein and

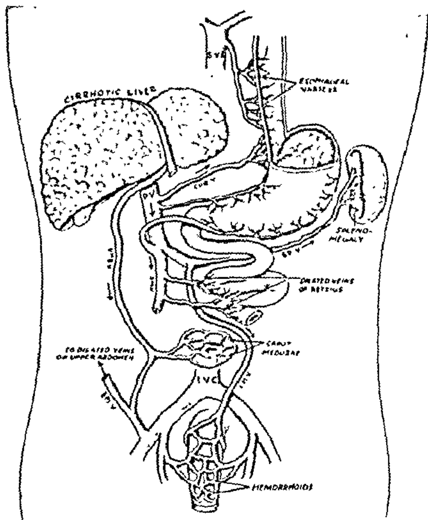


FIG 7 Collateral circulation with portal obstruction

tional to the intensity of the odor. Death often occurs within three to six months after this sign is noted. However, several patients with diffuse hepatic fibrosis have been followed for a period of five years after detecting a liver breath. Liver fetor disappears with improvement of general hepatic reserve

is a helpful adjunct. A radiologic diagnosis is possible in 60 to 80 per cent of cases of esophageal varices if barium sulfate is mixed with sodium methyl cellulose and films are obtained when the patient is bearing down while in a horizontal position. X-ray signs include filling defects, rounded expansions of mucosal folds, and scalloping of esophageal borders (Fig. 9)

Splenomegaly

Splenomegaly is an important accompaniment to liver disease An enlarged spleen may cause symptoms incident to its encroachment on other organs, produce an anemia, thrombocytopenia, and/or neutropenia, or rupture when traumatized It has been attributed to portal hypertension and passive congestion. Regenerative changes produce an enlarged and fibrotic spleen. Congestion or reticular hyperplasia may be also responsible When heart failure is associated with liver disease, splenomegaly has occurred as a result of peripheral emboli or splenic vein thrombosis Rarely, carcinomatous metastases to the liver interfere with portal blood flow and cause splenomegaly With improvement in fatty liver, viral hepatitis, passive congestion, and biliary hepatitis, an enlarged spleen often disappears, with diffuse hepatic fibrosis, splenic vein thrombosis, and carcinomatous metastases, it usually persists

The major effect of an enlarged spleen in liver disease is production of hypersplenic syndromes Cytopenia is associated with a hyperplastic bone marrow The cell type that is reduced peripherally is usually increased in the marrow Two mechanisms have been proposed to explain cytopenia (a) inhibition of the bone marrow by a humoral factor released from a hyperactive spleen (15), and (b) selective sequestration and phagocytosis by an abnormal spleen (16) The first thesis is supported by the finding of maturation arrest which disappears with splenectomy The demonstration of heavy concentration of radioactivity in the spleen, and abnormally little activity in the liver following transfusions with Cr^{51} tagged autogenous red blood cells in patients with cirrhosis and hemolytic anemia suggests that the spleen is the major site of red cell destruction

hepatic artery, and is dispersed through interlobular branches. These vessels communicate with the sinusoids and lead to central veins which drain into hepatic veins (Fig 8). An increase in portal blood pressure is responsible for collateral channels. Portal pressure may reach 250–600 ml H_2O Portal hypertension is due to mechanical interference with entry of blood into the liver by fibrous connective tissue or regenerated liver cells (9). Hypertension of the portal circuit and abdominal wall collaterals occurs secondary to extrahepatic phlebitis in the Cruveilhier-Baumgarten syndrome which is characterized by a caput medusae and a murmur and thrill over a patent umbilical vein (10).

Esophageal varices are the important collateral requiring treatment They are usually indicative of portal hypertension but may represent congenital venous anomalies, and have been demonstrated in congestive heart failure, viral hepatitis, and portal fibrosis in the absence of an elevated portal vein pressure (11). Both portal vein pressure measured directly and pressure obtained by wedging a catheter into a peripheral hepatic vein are elevated in patients with cirrhosis and esophageal varices (12). Hematemesis suggests the presence of varices in patients with liver disease, but other causes of gastrointestinal hemorrhage must be excluded The frequent association of chronic liver disease with peptic ulcer necessitates early differential diagnosis (13). A clinicopathologic study of five patients with nutritional cirrhosis, esophageal varices, and peptic ulcer demonstrates the need for evaluating such patients for hemorrhage from both of these sources Hemorrhage was attributed to bleeding varices in all of this group However, three patients succumbed to a bleeding duodenal ulcer

Esophagoscopy is valuable in recognizing esophageal varices It is a safe procedure, and if available, it is desirable to evaluate all patients with chronic liver disease for the presence of varices by this method Their size, extent of involvement, and condition of the overlying mucous membranes can be studied. Varices appear as clusters of soft bluish-gray or red veins. The venous pressure may be measured by a needle-manometer system attached to the esophagoscope (14). Barium study of the esophagus

Clinical features depend upon the degree and type of cytopenia Splenic neutropenia is characterized by recurrent infections, a white blood cell count between 1000 and 3000 per cu. mm, and increased granulocytes in the bone marrow Splenic thrombocytopenia due to liver disease may be difficult to distinguish from idiopathic thrombocytopenic purpura, although immunologic abnormalities appear to be responsible for the latter condition In both states there is purpura, a low platelet count, low prothrombin consumption time, a positive Rumpel-Leede test, decreased clot retraction, and increased megakaryocytes in the bone marrow Splenic anemia is associated with overt or subclinical evidence of hemolysis. There may be an anemia, icterus, reticulocytosis, and marked bone marrow erythropoiesis, or a lowered red blood cell count and decreased red cell survival may be the only manifestations of the condition Splenic pancytopenia is characterized by a combination of the described features of neutropenia, thrombocytopenia, and anemia

Mental Changes

Sensorial changes which include depression, somnolence, apathy, disorientation, agitation, delirium, and coma often develop in patients with impairment of hepatic function Mental alterations are frequently apparent in patients with hepatic cirrhosis They may be due to hepatic coma, delirium tremens, alcoholism, drugs, cerebrovascular disease, hypoglycemia, uremia, epilepsy, or functional psychoses

Hepatic coma usually appears in the terminal phase of liver disease It must be differentiated from coma which accompanies hypoglycemia, uremia, and drug intoxication Serial study has not demonstrated any specific physical signs, biochemical function tests, or histologic changes to account for the coma It has been attributed to an accumulation of abnormal metabolites (29) Laboratory studies show a normal cerebrospinal fluid pressure, increased spinal fluid protein, low serum electrolytes, and increased organic acids (pyruvic, ketoglutaric, and lactic) in many of these patients An elevated arterial ammonium level is usually present This is due to a lack of conversion of ammonia into



FIG. 9 Barium swallow demonstrating esophageal varices in patient with asymptomatic nutritional cirrhosis

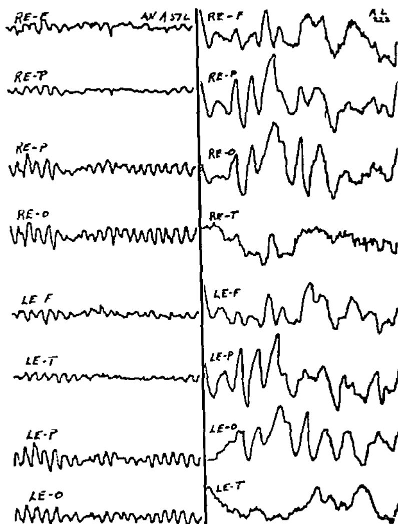


Fig 10 Normal electroencephalogram (right) compared with tracing in hepatic coma.

urea (30) because of shunting of blood past the liver or because of marked hepatic dysfunction. It has been suggested that this elevation is responsible for mental changes, although there may be increased serum ammonium level without cerebral dysfunction, and sensorial abnormalities are noted in the presence of a normal serum ammonium. This has been attributed to sampling of venous blood (31a, b) and technical difficulties in the chemical analysis (31c). Unlike the situation in health, there is a significant arterio-venous difference in the free ammonia content of the cerebral blood in patients with liver disease. It has been suggested that free ammonia is partly converted to glutamic acid in both brain and muscle due to its combination with ketoglutaric acid under the influence of glutamic dehydrogenase. Muscle removes approximately two times as much ammonia from the blood as the brain. Utilization of ketoglutarate causes sensorial changes because of disturbance of Krebs cycle and the consequent decrease in phosphorylation and oxygen utilization (31a, b). Sensorial changes accompanied by an elevation of serum ammonium occur in patients with hepatic disease who receive ammonium salts or resins (32), and following protein feeding in patients with naturally occurring or surgically induced portacaval shunts.

Histologic study may show evidence of brain atrophy or hemorrhagic encephalopathy. In most instances, however, no morphologic lesion is present to account for mental alterations. Hepatic coma is precipitated by many distinct situations including hemorrhage, infection, depressant drugs, and electrolyte disturbances. When these factors serve as trigger mechanisms sensorial changes may be transient or foreshadow death, depending upon the degree of hepatic reserve. Mild to moderate hemorrhage, a single dose of a barbiturate or morphine, or a viral respiratory infection is often followed by coma in patients with severe hepatic insufficiency, whereas no adverse response is noted in patients with compensated liver disease.

Impending hepatic coma is characterized by pronounced slowing of normal mental processes, disorientation, and confusion. In the initial phase, drowsiness and lethargy, or restlessness and agitation are present. A "flapping" tremor is noted when the patient

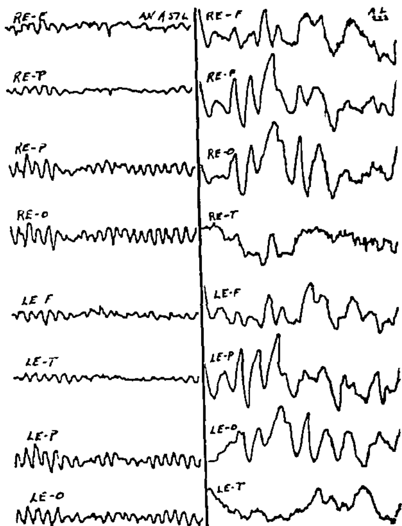


FIG 10 Normal electroencephalogram (right) compared with tracing in hepatic coma

holds his arms forward with hands and fingers extended for a short period. It is characterized by coarse, irregular, flexion–extension movements of the fingers and wrists. Occasionally, the lower extremities and facial area are involved. These tremors are accompanied by hyperactive reflexes and may be followed by bilateral extensor plantar responses. Electroencephalographic tracings show bilateral synchronous slow waves of 2–3/second, most marked in the frontal area (Fig. 10). Triphasic waves appear when coma supervenes (33).

NONSPECIFIC SIGNS OF LIVER DISEASE

Fluid Retention and Electrolyte Disturbances

Liver dysfunction is accompanied by subclinical or clinical evidence of abnormal fluid retention. Dilution technics demonstrate an increase in total body water by deuterium oxide or antipyrine methods (17), and expansion of extracellular water by inulin or sucrose methods (18). There is a variable effect on the intracellular water, calculated as the difference between total body water and the extracellular water, and plasma volume determined by Evans blue or iodinated serum albumin (19).

Overt manifestations of fluid accumulation include peripheral edema, pulmonary congestion, ascites, and/or hydrothorax. Ascites is the most frequent, and often the only clinical evidence of fluid imbalance. Ascites decreases respiratory reserve and predisposes to pulmonary infection. Abdominal localization is due to a difference in the rate of inflow and outflow of fluid from the peritoneal cavity. Radioactive tracer studies show an exchange of 40–80 per cent of peritoneal fluid every hour (20). Entry of fluid into the peritoneal cavity is increased by mechanisms which reduce renal excretion of sodium and water. Outflow of ascitic fluid is decreased by hypoalbuminemia, lymph stasis, and venous hypertension.

Ascites can be correlated with the severity of liver injury. Thus, in nutritional liver disease only 5 per cent of the patients with fatty liver have ascites, whereas, over 50 per cent of those with diffuse fibrosis show this sign. Abnormal salt and water reten-

tion is responsible for clinical ascites, although its mechanism is unknown. There is decreased excretion of sodium into the urine, sweat, saliva, and stools, as a result of pituitary–adrenal changes and other factors not yet clarified (21) Adrenal salt-retaining hormones have been isolated from the urine and serum of such patients. Estrogens and androgens given to patients with hepatic cirrhosis and ascites increase salt and water retention and it has been suggested that abnormal metabolism of these hormones may be a factor in fluid retention of liver diseases (22)

In advanced liver disease total 24-hour urine sodium excretion is sometimes only 10 per cent of normal There is frequently an independent decrease in capacity to excrete water which further increases fluid retention and occasionally leads to syndromes of water intoxication Serum protein levels, portal hypertension, hepatic venous obstruction, intra-abdominal tension, and lymph stasis are important contributing factors (22) Any of these conditions may individually play a major role in formation or maintenance of ascites Hypoalbuminemia facilitates fluid accumulation by reduction of colloidal osmotic pressure Portal hypertension and obstruction of the hepatic venous bed (23) accelerate transudation of plasma filtrate by increasing hydrostatic pressure Intra-abdominal tension further distorts intravascular pressure relationships, and abnormal lymphatic drainage prevents a return of extravasated fluid to the plasma

The chemical composition of ascitic fluid depends upon the degree of lymphatic block, and previous fluid loss Usually the fluid is a clear yellow transudate with a protein content of 0 2–0 03 mEq /100 cc, and a sodium content of 150–180 mEq 100 cc Occasionally, it is turbid or milky due to a lipoprotein complex or fat globules

Patients with liver disease in whom abnormal fluid accumulation is limited to the chest present a problem in diagnosis Such pleural effusion is often due to inflammatory or neoplastic pulmonary disease At times, no cause besides hepatic disease can be found, and with improvement in liver functions, accumulated fluid disappears It has been suggested that pleural effusion in these instances results from either (a) passage of fluid from the

abdominal cavity, by way of the lymphatic vessels of the diaphragm, or (b) intrathoracic exudation of fluid due to an increase in pressure in the azygos vein (21).

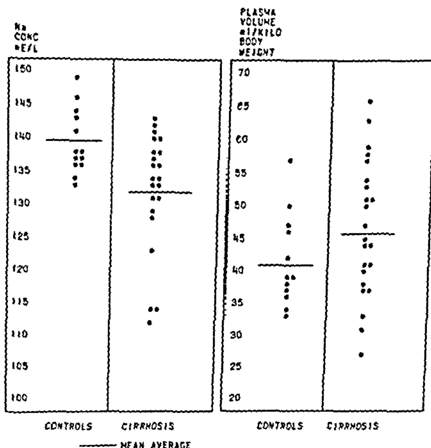


FIG 11 Serum sodium concentration and plasma volume studies in nutritional cirrhosis with fluid retention demonstrating a wide range of values

Plasma sodium, interstitial sodium, and intracellular sodium tend to be altered in chronic liver disease. Body salt depletion, hemodilution, and shifts of extracellular sodium into the cells all tend to alter normal distribution of this ion. In some instances of fluid retention refractory to therapy, a complete evaluation of body sodium content and *distribution is important. Simultaneous*

estimation of plasma volume and serum sodium concentration provides an index to the total circulating sodium (Fig. 11). Circulating sodium is normally 6.0 ± 0.7 mEq/Kg body weight, and may vary from a low of 3.0 mEq/Kg in salt depletion to a high of 13 mEq/Kg in salt intoxication. The total circulating sodium may permit differentiation of hyponatremia due to salt depletion and primary water retention when one of these mechanisms is principally responsible for a decrease in concentration of serum sodium. It facilitates recognition of plasma sodium deficits with normal serum concentration of this ion. It is a practical procedure readily available in most hospitals (25). Extracellular sodium is determined by a combination of inulin and serum sodium studies, intracellular sodium is derived by subtracting extracellular sodium from total exchangeable sodium measured by Na^{24} dilution (26).

Similar alterations in body potassium are noted in hepatic insufficiency. A reduction in serum potassium occurs with plasma dilution, excess potassium losses in the stool or urine, acid-base disturbances, and after prolonged use of parenteral fluids which do not contain potassium (27). An elevated serum potassium is seen when liver disease is complicated by shock or uremia. Intracellular potassium is frequently low due to deficient protein and glycogen stores, dehydration, acid-base disturbances, and/or a deficient potassium intake. Total body potassium and its distribution may be determined by using dilution technics for compartment analysis along with serum potassium, and total exchangeable potassium (28).

Abnormal serum magnesium, calcium, phosphorus, zinc, and copper levels have been found in patients with liver disorders. Magnesium deficiency is frequent in chronic alcoholic patients with hepatic disease. The normal value for serum magnesium varies between 1.7 and 2.3 mg per cent, depending upon the method used. Low levels may be responsible for muscle twitching, tremors, or convulsions (28).

Hormonal Disturbances

The liver is responsible for the interconversion, synthesis and/or degradation of many hormones. Hepatic disease may cause any type of hormonal imbalance. The number and site of functional

groups, the geometry of the molecule, and the state of oxidation, all of which are influenced by hepatic activity, are important in determining the physiologic activity of steroids (34). Clinical studies have demonstrated abnormalities in estrogen, androgen, adrenal steroid, and thyroid metabolism secondary to hepatic disease. Hepatic dysfunction is frequently present in patients with primary endocrinopathies who have intercurrent nutritional problems.

Abnormal estrogen metabolism is the most commonly encountered hormonal derangement in liver disease. It may produce menstrual disturbances, gynecomastia, testicular atrophy, changes in body hair and contour, and decrease in libido. Laboratory studies often show an increase of estrogenic substances in urinary output, and decreased excretion of androgens and other ketosteroids (35). The liver normally removes estrogens from the blood, inactivates them, and excretes them into the bile (35). They are reabsorbed from the bile and undergo an enterohepatic circulation. They are conjugated in the liver, chiefly as glycuronates and sulfates, and are converted from the less potent state of estrone to estradiol.

Amenorrhea or hypermenorrhea is often present in women with nutritional liver disease. It is difficult to decide whether these changes are part of hepatic disease or due to malnutrition. Hormone excretion studies are not correlated with the degree of liver injury, severity of malnutrition or type of menstrual disturbance. Hepatic insufficiency is usually characterized by amenorrhea. However, hypermenorrhea does occur sometimes and may constitute a major problem. Alteration in the estrogen level is the chief factor responsible for excessive bleeding. Bleeding may occur from either a hypoplastic or hyperplastic endometrium, and continues until sufficient estrogen is produced to cause endometrial regeneration. Other factors such as thrombocytopenia, increased capillary fragility, and clotting abnormalities intensify hemorrhage. Improvement in hepatic reserve rectifies the endocrine abnormality and permits restoration of normal menstrual patterns.

Gynecomastia occurs in 7–10 per cent of male patients with

moderate to severe liver disease. Enlarged breasts are tender, show pigmented areolae and erect nipples, and at times elaborate a secretion Biopsy may be required to exclude malignancy Histologic sections show proliferation of connective tissue, increased number of ducts, periductal infiltration of lymphocytes, and other cellular elements, and dilatation of lactiferous sinuses (36). We have noted gynecomastia in patients with hepatic fibrosis, chronic viral hepatitis, neoplastic infiltration of the liver, fatty liver, and hepatic congestion in heart failure It has not been possible to correlate the condition with the severity of hepatic dysfunction (36) Both unilateral and bilateral gynecomastia have regressed with improvement in hepatic reserve Most instances of gynecomastia in hepatic disease result from failure of the liver to inactivate estrogens or estrogen-like substances However, increased production of estrogens by the adrenal, testicular failure with decreased production of androgens, and increased elaboration of breast-stimulating materials by the pituitary may be contributory (37) Hormonal studies have shown an elevated urine estrogen with normal urinary androgens and 17-ketosteroids in most patients In one case of nutritional cirrhosis associated with gynecomastia studied in our clinic, the 17-ketosteroids were elevated to twice the normal values and returned to normal with improvement in hepatic function

Testicular atrophy and a history of impotence are frequently present in men with severe liver disease Histologic study of postmortem specimens has revealed atrophy of the germinal epithelium, decrease in the diameter of seminiferous tubules and interstitial fibrosis Testicular dysfunction appeared to be secondary to a high level of body estrogen which was accompanied by decreased excretion of pituitary gonadotrophin and a low level of androgen (38).

Clinical signs of adrenal hypofunction reflected in marked asthenia, hypotonia, and skin pigmentation occur in an occasional patient with liver disease Reduced excretion of hydroxycorticosteroids and 17-ketosteroids and diminished blood eosinophile and ketosteroid response to ACTH are sometimes observed without clinical symptoms of adrenal disease Atrophy of the

adrenals with reduction of its lipid content has been noted in postmortem studies of patients with liver disease. On the other hand, hirsutism, acne, purplish, striae, hypertension, hyperglycemia, and increased urinary corticoid excretion suggestive of Cushing's syndrome were encountered by Bongiovanni and Eisenmenger (39). Metabolism of adrenal corticoids is dependent upon an intact liver. The disappearance of 17-hydroxycorticosteroids (hydrocortisone) from the plasma of patients with liver disease is inversely proportional to the degree of liver damage measured by bromsulfalein retention (40). Hepatic dysfunction is accompanied by prolonged elevation of blood levels of adrenal steroids and decreased urinary excretion of their waste products.

Blood Pressure and Vascular Changes

Current theories on the cause of hypertension and shock all include the liver. It has been demonstrated that experimental renal hypertension is eliminated by hepatic injury. Goldblatt has postulated that hypertension results from the interaction of renin produced in the kidney, and hypertensinogen elaborated in the liver (41). Shorr proposed that the kidney produces a vasoexcitor substance (VEM) which is opposed by a vasodepressor substance (VDM) manufactured in the muscles and the liver; VEM ordinarily predominates to maintain normal blood pressure levels (42). Inhibition of the normal hepatic process of deactivation of VDM causes hypotension and shock.

A low incidence of hypertension has been recorded in studies of patients with severe liver disease (43). Of 250 patients with hepatic cirrhosis due to nutritional deficiency observed in our clinic, 70 per cent had normal blood pressure, 4 per cent had hypotension, and 26 percent had hypertension. A serial study of 38 hypertensive patients who developed progressive hepatic insufficiency revealed an increase in hypertension in 5 (13.1 per cent), decrease in 19 (50 per cent), no change in 8 (21.0 per cent), and marked fluctuations in 6 (15.7 per cent). The following case history is illustrative of the decrease in blood pressure which occurred with severe hepatic damage in one half of our hypertensive patients.

CASE 2 DISAPPEARANCE OF HYPERTENSION WITH PROGRESSIVE HEPATIC INSUFFICIENCY

Clinical Features W.C., a 64-year-old laborer, had documented hypertensive heart disease for a period of 10 years, with blood pressure ranging between 180/110 and 196/140, associated with an enlarged heart, retinopathy, and renal dysfunction

He developed biliary cirrhosis as a result of prolonged common duct obstruction, and serial recordings showed a gradual reduction of his blood pressure to 120/80 At abdominal exploration, gallstones were found to be responsible for biliary obstruction The liver was green, firm, and finely nodular Postoperatively, the patient's blood pressure remained within the normal range and cardiomegaly and eyeground changes decreased There was no evidence of myocardial infarction, a

Biochemical study	*At time of surgery*	*Eight months later*
Serum bilirubin (mg %)	6 0	0 8
Alkaline phosphatase (B U)	5 5	7 5
Bromsulfalein (%)		42 5
Total serum cholesterol (mg %)	213	253
Cholesterol esters (mg %)	130	162
Serum albumin (gm %)	3 1	3 5
Serum globulin (gm %)	4 5	4 8
Cephalin flocculation	3 +	3+
Thymol turbidity (units)	5 0	4 5
Prothrombin time	12 8/12 3	15 15
Histologic study	*At time of surgery*	*Eight months later*
Fibrosis	2+	2+
Fat	0	0
Regeneration	3+	3+
Bile stasis	2+	0
Infiltration	2+	1+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	*Biliary cirrhosis*	*Biliary cirrhosis*

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of 30 mg/100cc and 35 mg/100cc had no clinical stigmas and only minor biochemical functional changes to indicate hepatic disease was responsible Hypoglycemia due to liver disease must be differentiated from that due to pancreatic, adrenal, pituitary, or thyroid disease (47). We have seen it most commonly in patients with fatty liver and nutritional cirrhosis However, it is also seen in patients with hepatic congestion due to heart failure, fulminant viral hepatitis, and carcinomatous metastases to the liver.

The carbohydrate disturbance is usually the primary abnormality in patients with liver disease who have hyperglycemia and glycosuria In these instances, hepatic changes are usually secondary to poor nutrition Hyperglycemia and glycosuria may coexist with liver disease without evident nutritional abnormalities. The diabetic develops his share of liver changes due to congestive heart failure, metastatic malignancy, viral hepatitis, and biliary obstruction. Hemochromatosis is accompanied by liver and pancreatic lesions, both of which may contribute to carbohydrate disturbance Occasionally, pancreatitis is associated with liver injury and hyperglycemia and glycosuria Normal carbohydrate tolerance depends upon the integrity of the liver Intravenous glucose tolerance tests have resulted in three general patterns in liver disease a flat curve in 30 per cent, a diabetic-like curve in 18 per cent, and a normal curve in 32 per cent of 100 nonselected patients with nutritional cirrhosis Patients with decompensated cirrhosis frequently have a flat or diabetic-like curve, whereas normal curves are usually present in cirrhosis without jaundice, fluid retention, or sensorial disturbances

A diabetic-like syndrome resulting from liver disease is difficult to establish apart from true diabetes mellitus (48) We have employed the following criteria (a) history of exposure to hepatotoxins or of liver injury prior to the appearance of the diabetic syndrome, (b) clinical, biochemical, or histologic evidence of liver disease, (c) lack of familial history of diabetes or clinical evidence of pancreatic, pituitary, adrenal, or thyroid disease, (d) disappearance of hyperglycemia and glycosuria without insulin with improvement of hepatic function, and (e) normal

cerebrovascular episode, or other specific mechanism to account for reduction in blood pressure.

Comment. The decrease in blood pressure and improvement in clinical stigmas of hypertensive vascular disease noted in this patient was not accompanied by malnutrition and favors the thesis that liver cell injury may induce hypotension. Improvement in hepatic reserve may be followed by return of blood pressure readings to previous levels. Although jaundice disappeared in this patient, there was little alteration in biochemical and histologic abnormalities.

There has been considerable interest in the possible relationship between atherosclerosis and liver disease. Instances of decreased incidence of atherosclerosis in patients with nutritional cirrhosis and an increase in biliary cirrhosis have been reported. A rough correlation has been noted between atherosclerosis and the serum cholesterol, cholesterol-phospholipid ratio (44), and serum lipid fractionation by ultra centrifugation (45). In our investigations, there appears to be no significant decrease in the incidence of atherosclerosis in patients with liver disease. Nine per cent of cases of advanced nutritional cirrhosis studied at autopsy had significant coronary atherosclerosis. Several patients had been observed with classic clinical and electrocardiographic criteria for a diagnosis of myocardial infarction. Serial electrocardiograms and ballistocardiograms in patients with liver disease have occasionally demonstrated evidence of coronary artery disease unsuspected by history and physical examination.

Blood Sugar Disturbances

The fasting blood sugar level is usually normal in liver disease (46). Hypoglycemia or hyperglycemia may be observed. Hypoglycemia is usually associated with nervousness, increased sweating, palpitations, aberrant behavior, convulsions, or coma. A low blood sugar is related to a decreased intake of carbohydrate associated with an abnormality in glycogenolysis, glycogenesis, gluconeogenesis, or a combination of these factors. The degree of hypoglycemia cannot be correlated with the results of biochemical liver function studies or morphologic changes of the liver. Two patients with fatty liver admitted with blood sugars

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response to the provocative cortisone–glucose tolerance test after disappearance of evidence of acute liver injury.

Fourteen patients with suspected hepatic diabetes have been evaluated in our clinic. Seven had nutritional cirrhosis and seven had fatty liver. Therapeutic response suggests that hyperglycemia resulted from disturbance of hepatic homeostasis of blood sugar in eight patients, and from the unmasking of latent diabetes in four patients. The mechanism was obscure in two patients who developed insulin resistant diabetes. Giving 125 mg of cortisone in two divided doses, one at six hours and one at one hour, prior to a standard glucose tolerance test, facilitates the diagnosis of latent diabetes. Cortisone in such cases produces a typical diabetic tolerance curve. Significant ketosis has not been observed although patients have consumed large quantities of alcoholic beverages, eaten poorly, and received no insulin. None of the patients had clinical evidence of accelerated vascular disease. The differential diagnosis of hepatogenic diabetes and diabetes mellitus with secondary liver changes was most readily made by prolonged therapeutic observation. Prognosis for both the liver changes and the carbohydrate disturbances was good with proper treatment. Six patients returning to alcoholism and poor dietary habits had re-occurrence of hyperglycemia and glycosuria. Clinical abnormalities were controlled in eight patients adhering to their therapeutic regimen.

Renal Abnormalities

Renal dysfunction is frequently present in patients with hepatic disease. In many instances, hepatic and renal disease occur as independent phenomena (49). A common mechanism is responsible for encountered hepatic and renal abnormalities in choline deficiency (50), and toxic injury to the liver and kidney. The hepatorenal syndrome is characterized by necrosis of the liver cells with secondary lesions of the renal tubules (51). Patients with liver disease who develop shock as a result of portal vein thrombosis, overwhelming infection, or massive gastrointestinal hemorrhage have renal failure. Rarely, hepatic dysfunction accompanies inflammatory or nutritional changes which occur in primary kidney disease.

Renal function abnormalities may cause azotemia, clearance abnormalities, and/or pathologic urine constituents Blood urea is largely synthesized in the liver and, therefore, tends to be reduced in patients with acute hepatic insufficiency We have noted varying degrees of azotemia in decompensated patients with nutritional cirrhosis. Elevation of blood urea also occurs in patients with fatty liver, viral hepatitis, and biliary obstruction Azotemia is usually transient and related to dehydration or hemorrhage It may represent a terminal manifestation or occur as a result of bile nephropathy, "acute tubular necrosis," pyelonephritis, or glomerulonephritis.

Inulin and para-aminohippurate clearance studies conducted in our clinic have been normal in patients with fatty liver and mild nutritional cirrhosis However, a decreased renal plasma flow and increased tubular reabsorption are usually present in patients with cirrhosis and ascites (52) These abnormalities diminish with improvement of hepatic function Microscopic urinalysis frequently reveals casturia and an increased number of red and white blood cells These findings are most prominent in patients with acute liver injury accompanied by jaundice Transient albuminuria occurred in one half of the patients we have studied with fatty liver, one third of those with nutritional cirrhosis, one third of those with biliary hepatitis, and one fifth of the patients with viral hepatitis

Kidney biopsies on patients with nutritional liver disease in the Jersey City Medical Center have not demonstrated any morphologic abnormalities except where there is independent renal disease Histologic study of the kidney is a valuable diagnostic adjunct in patients with hepatorenal syndromes where the etiology is not clear. Specific changes may be seen in the nephrotic syndrome, lower nephron nephrosis, lupus erythematosus, and other renal lesions

Hematologic Syndromes

Anemia or a hemorrhage diathesis is present in one third of cases of chronic liver disease Such patients exhibiting anemia should have a red blood cell count, hematocrit, and blood smear to determine the cause, severity, and morphologic characteristics.

response to the provocative cortisone-glucose tolerance test after disappearance of evidence of acute liver injury.

Fourteen patients with suspected hepatic diabetes have been evaluated in our clinic. Seven had nutritional cirrhosis and seven had fatty liver. Therapeutic response suggests that hyperglycemia resulted from disturbance of hepatic homeostasis of blood sugar in eight patients, and from the unmasking of latent diabetes in four patients. The mechanism was obscure in two patients who developed insulin resistant diabetes. Giving 125 mg. of cortisone in two divided doses, one at six hours and one at one hour, prior to a standard glucose tolerance test, facilitates the diagnosis of latent diabetes. Cortisone in such cases produces a typical diabetic tolerance curve. Significant ketosis has not been observed although patients have consumed large quantities of alcoholic beverages, eaten poorly, and received no insulin. None of the patients had clinical evidence of accelerated vascular disease. The differential diagnosis of hepatogenic diabetes and diabetes mellitus with secondary liver changes was most readily made by prolonged therapeutic observation. Prognosis for both the liver changes and the carbohydrate disturbances was good with proper treatment. Six patients returning to alcoholism and poor dietary habits had re-occurrence of hyperglycemia and glycosuria. Clinical abnormalities were controlled in eight patients adhering to their therapeutic regimen.

Renal Abnormalities

Renal dysfunction is frequently present in patients with hepatic disease. In many instances, hepatic and renal disease occur as independent phenomena (49). A common mechanism is responsible for encountered hepatic and renal abnormalities in choline deficiency (50), and toxic injury to the liver and kidney. The hepatorenal syndrome is characterized by necrosis of the liver cells with secondary lesions of the renal tubules (51). Patients with liver disease who develop shock as a result of portal vein thrombosis, overwhelming infection, or massive gastrointestinal hemorrhage have renal failure. Rarely, hepatic dysfunction accompanies inflammatory or nutritional changes which occur in primary kidney disease.

peripheral neuritis due to nutritional deficiency Adequate erythrocytic maturing factor is usually present, and extracts of the most extensively damaged liver initiate good hematologic response (55). Response to Co^{60}, labeled B_{12}, given orally (Schilling test) is of great value in differential diagnosis

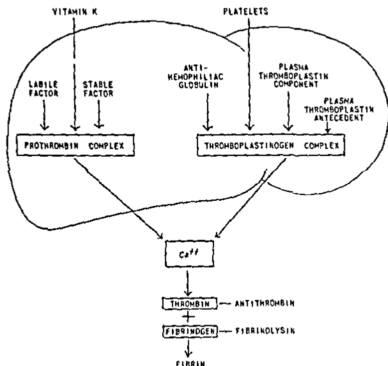


FIG 12 Diagrammatic representation of the role of the liver in blood coagulation (after Sussman)

Bleeding tendencies characterized by petechiae, purpura, epistaxis, bleeding gums, melena, etc are often found in patients with moderate to severe hepatocellular disease This is reasonable in view of the importance of the liver in maintaining normal hemostasis (Fig 12) *Currently available laboratory studies* facilitate delineation of the mechanisms responsible for abnormal

It may be necessary to evaluate the bone marrow, conduct red cell survival studies, and assay the serum and red cells for hemolysis.

Anemia is due to decreased production, increased loss, or excessive destruction of erythrocytes. A combination of blood loss, nutritional deficiency, abnormal splenic function, and infection is often responsible for anemia in hepatic disease. Studies of red blood cell survival by the Ashby technic and radioactive chromium show subclinical hemolysis is the most frequent cause of anemia in the absence of blood loss (53). This appears to be due to local destruction of red cells, probably through their sequestration in the spleen. There is often an accompanying erythroblastosis of the bone marrow, increased urine urobilinogen, and reticulocytosis. In health, the normal rate of hemoglobin production is approximately 0.09 gm./Kg. of body weight/day. A variety of chronic diseases are associated with decreased red cell survival but increased amounts of hemoglobin are produced to maintain an equilibrium. Anemia usually develops when the mean life span of the erythrocytes is less than 15–20 days. Occasionally, acute hemolytic anemia with a positive Coombs test may occur (54). Morphologic studies on 114 of our patients with moderate to severe nutritional cirrhosis showed a normochromic normocytic anemia in 63 per cent, a macrocytic hyperchromic anemia in 30 per cent, and a microcytic hypochromic anemia in 7 per cent.

Normocytic normochromic anemia occurs in patients with low-grade hemolysis and acute blood loss. Microcytic hypochromic anemia is seen with decreased dietary intake of iron and with pathologic bleeding from esophageal varices, hemorrhoids, or other sources. Macrocytic anemia is commonly due to subclinical hemolysis but may result from a deficiency of folic acid or vitamin B_{12}. Folic acid deficiency is suggested by leukopenia, large granulocytes in the peripheral blood showing peculiarities of nuclear chromatin, and a low reticulocyte count. Macrocytosis may be present in cirrhosis with and without anemia. Pernicious anemia is occasionally simulated because of megaloblastosis of the bone marrow, decreased or absent hydrochloric acid, and

peripheral neuritis due to nutritional deficiency. Adequate erythrocytic maturing factor is usually present, and extracts of the most extensively damaged liver initiate good hematologic response (55). Response to Co[60], labeled B_{12}, given orally (Schilling test) is of great value in differential diagnosis.

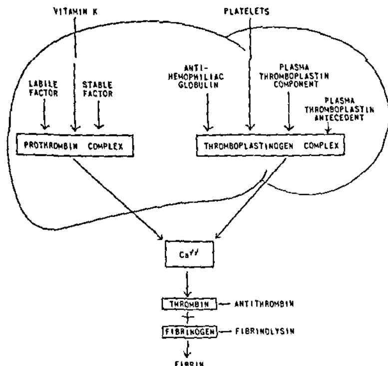


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hemorrhage in the individual patient. Bleeding tendencies in liver disease are usually due to increased capillary fragility, hypoprothrombinemia, thrombocytopenia, or low fibrinogen. Rarely, there may be an abnormality in plasma or serum acceleration factors, antihemophiliac globulin, or fibrinolytic and antithrombin activity.

Capillary fragility is frequently related to vitamin C deficiency and may be evaluated by the Rumpel-Leede test. Hypoprothrombinemia due to an inability to produce prothrombin or labile factor is the most common coagulative deficiency in liver disease. Manufacture of prothrombin requires an adequate supply of vitamin K and the functional integrity of liver cells, in addition to the labile factor (accelerator globulin) and stable factor (serum accelerator factor). Thrombocytopenia presumably due to splenic hyperactivity is reflected in abnormal bleeding time, clot retraction, and prothrombin consumption. According to Stefanini (56), platelets supply: (a) platelet thromboplastic factor which activates thromboplastin from an inactive plasma precursor, (b) platelet factor 1 which accelerates the conversion of prothrombin to thrombin, (c) platelet factor 2 which accelerates the conversion of fibrinogen to fibrin; and (d) platelet factor 3 which opposes the activity of heparin. Agglutination of platelets begins hemostasis by providing a vasoconstricting agent, initiates blood coagulation by supplying its thromboplastic factor, and secures permanent hemostasis by effecting clot retraction.

ACCOMPANYING CONDITIONS

Hypovitaminosis

Clinical syndromes due to vitamin deficiency in liver disease can be attributed to an inadequate diet in most instances. In cases with biliary obstruction, a deficiency of fat-soluble vitamins is a result of decreased fat absorption.

Thiamine hydrochloride deficiency is the most frequently encountered vitamin imbalance. It contributes to fatigue and weakness, and is responsible for peripheral neuritis. Rarely, there is associated beriberi heart disease. Alcoholic patients are not

infrequently seen with an enlarged heart, fluid retention, and fatty liver in which a high protein and thiamine hydrochloride intake cause a disappearance of these abnormalities. Mild to moderate niacin deficiency is common, and a full-blown picture of pellagra is sometimes present

Vitamin A ...

disease w

these vit. ... poor dark adaptation are encountered in a large percentage of alcoholics with nutritional cirrhosis It occurs less often during the course of other causes of cirrhosis Full-blown scurvy is occasionally present in patients with decompensated cirrhosis

Reactions to Infections

There appears to be an increased susceptibility to infections in patients with liver disease. Symptoms and signs of a febrile illness appear when an infection is responsible for liver injury, an inflammatory process accompanies liver cell necrosis, or there is an intercurrent or concurrent infectious disease The liver normally helps control systemic infections by removing bacteria from portal venous blood and producing antibodies Hepatic blood flow increases threefold with infection (57), and approximately 60 per cent of the bacteria passing through the liver are removed (58) Opsonins, immune bodies, complement, and antitoxin depend on an intact liver for their production Inability to produce normal amounts of these substances predisposes to recurrent infections

Infections resistant to antibacterial agents are often directly responsible for death in hepatic insufficiency Careful bacteriologic study including antibiotic sensitivity is important in these patients Liver disease does not interfere with the ability of the body to handle chemotherapeutic agents or antibiotics Immunization is achieved with the same facility as in normal individuals, except where there is a deficiency of gamma globulin which is rarely seen in chronic liver disease

Superimposed infections often have a deleterious effect on hepatic reserve Intercurrent infections in patients recovering

hemorrhage in the individual patient. Bleeding tendencies in liver disease are usually due to increased capillary fragility, hypoprothrombinemia, thrombocytopenia, or low fibrinogen. Rarely, there may be an abnormality in plasma or serum acceleration factors, antihemophiliac globulin, or fibrinolytic and antithrombin activity.

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ity changes and neuroses often represent latent emotional disturbances which are aggravated by hepatic disease Psychological testing of a group of chronic alcoholic patients with liver disease being followed in our clinic showed personality alterations which included psychoneurosis, character disorders, and psychoses. Organic psychoses are characteristic of terminal phases of liver insufficiency and are occasionally noted in viral hepatitis and nutritional cirrhosis

Focal brain hemorrhage of a nonspecific nature and location is found in patients dying in hepatic coma The hemorrhage contributes to observed psychoneurotic or psychotic symptoms, hyperactivity of deep tendon reflexes, extensor plantar response, choreiform movements, Parkinsonian tremors, and electroencephalographic changes

Peripheral neuritis and myelopathy are seen in liver disease due to nutritional disturbances, similar neuritic changes have been noted in patients with fulminant viral hepatitis Hepatolenticular degeneration is associated with amino aciduria and an error in copper metabolism which are presumably responsible for liver injury, basal ganglion disease, and the Kayser-Fleischer ring seen in this disease

Neurologic and psychiatric disease may be complicated by secondary liver pathology due to nutritional alterations This is occasionally of major concern in the paraplegic and quadriplegic patient, where food absorption may be altered because of the neurologic lesion

Constitutional Symptoms

Both acute and chronic liver disease are accompanied by such nonspecific symptoms as anorexia, weight loss, weakness, and malaise which may be related to toxemia or reflect metabolic disturbances incident to hepatic dysfunction Loss of appetite occurs predominantly in acutely ill patients with icterus, ascites, and sensorial changes It is rarely due to an enlarged liver which mechanically compresses the stomach Weight loss results from inadequate food intake, inability to assimilate food stuffs, and negative nitrogen balance

Weakness and malaise sometimes constitute the chief complaints

from viral hepatitis produce an exacerbation of symptoms and biochemical abnormalities. Minor infections in patients with severe hepatic disease may precipitate hepatic coma.

Reactions to Surgical Trauma

Surgical trauma is accompanied by measurable biochemical and histologic changes in the liver. Biochemical study shows bromsulfalein retention, bilirubin elevation and a positive cephalin flocculation test. Serial biopsy demonstrates intralobular and perilobular infiltration of polymorphonuclear leukocytes, monocytes, and lymphocytes. These changes subside quickly and are not usually associated with clinical abnormalities, although they interfere with intermediary metabolism. Similar biochemical and histologic alterations have been noted in battle casualties. Most patients undergoing surgery develop increased plasma levels of 17-hydroxycorticosteroids (40) due to a combination of liver dysfunction and activation of the pituitary–adrenal axis. This contributes to the sodium and water retention, negative nitrogen and potassium balance, eosinopenia, creatinuria, and decreased phagocytosis seen in postoperative states.

Surgical procedures in patients with liver disease may be deleterious. Hepatic coma frequently results from major operative procedures in patients with borderline hepatic insufficiency. Careful preoperative and postoperative attention to the hepatic status and limitation of anesthetic and surgical trauma reduces morbidity and mortality. A study of surgical convalescence in 30 patients with nutritional cirrhosis in our clinic demonstrated a correlation of morbidity and mortality with the severity of liver disease and the extent of surgery. Patients with mild to moderate cirrhosis had negligible morbidity and no mortality from operative trauma, whereas 20 per cent of those with severe cirrhosis died following major surgical procedures.

Neurologic Changes

A variety of psychiatric and neurologic syndromes are observed in patients with liver disease. Appropriate examinations are indicated and include psychiatric and neurologic evaluation, skull x-rays, electroencephalography, and spinal fluid study. Personal-

abnormal liver function tests reflect nutritional, noxious, or vascular changes which require therapy This is illustrated in patients who undergo surgical procedures or develop curable medical illnesses Even the most minor stress is accompanied by hepatic dysfunction as determined by sensitive biochemical tests. The circulating level of adrenocortical hormones is regulated in part by the functional state of the liver and many of the effects of increased production of 17-hydroxycorticosteroids depend upon a combination of adrenal and hepatic reserve.

In a group of 180 patients with subclinical liver disease, biochemical abnormalities were associated with normal liver histology in 50 per cent, histologic changes were the only abnormal finding in 30 per cent, and a combination of biochemical and histologic changes was present in 20 per cent The more sensitive liver function tests such as bromsulfalein excretion and cephalin flocculation were abnormal Histolgic changes included fatty metamorphosis, lymphocytic infiltration, focal necrosis, iron deposition, and localized fibrosis

Acute anicteric viral hepatitis often falls into the category of subclinical liver disease and is recognized with difficulty unless it occurs as a part of an epidemic The presence of vague constitutional symptoms such as fatigue, abdominal distress, or general malaise accompanied by a positive flocculation test and bromsulfalein retention which gradually returns to normal is suggestive, and may provide the only clue to the diagnosis unless a liver biopsy is performed

A diagnosis of subclinical liver disease in the individual patient may be questioned because (a) biochemical liver function tests are nonspecific, (b) histologic changes may not be significant, and (c) there is often a poor correlation among clinical biochemical, and histologic findings The general concept of subclinical liver disease is useful when improvement in biochemical and anatomic abnormalities, under therapy, is accurately noted (59) Care must be taken in differentiating subclinical liver disease from psychoneurosis cholecystitis virus pneumonia, metastatic cancer, collagen disease, etc , where hepatic factors do not contribute to the encountered symptom complex

in patients with both active and inactive hepatic disease. Muscular weakness has been attributed to disuse atrophy of bed rest and an abnormality in energy metabolism imposed by nutritional deficiency or interference with enzyme systems. This often presents a problem in differential diagnosis and is discussed further in Chapter Five.

Subclinical Liver Disease

Hepatic abnormalities may be present without clinical signs or symptoms. The diagnosis of liver disease in these circumstances is based on biochemical and histologic findings. Subclinical changes are usually of minor significance but may be the only reflection of severe hepatic disease. Liver disease is characterized at its onset by biochemical and or histologic changes without clinical abnormalities Patients with reversible hepatic disease pass through a subclinical recovery period where signs and symptoms disappear but biochemical and histologic alterations persist.

Most studies of subclinical liver disorders have been made in patients with extrahepatic disease Subclinical alterations occur commonly in. (a) nutritional disturbances such as protein deficiency, vitamin deficiency, starvation, and obesity; (b) metabolic abnormalities including diabetes mellitus, acid-base disturbances, gout, and functional hypoglycemia, (c) conditions associated with alteration of blood flow and oxygenation of the liver as anesthesia, surgical trauma, shock, and anemia; (d) states leading to activation of the phagocytic and defense mechanisms of the liver as x-ray therapy, bacteremia, malaria, brucellosis, pneumonia, rheumatoid arthritis, Boeck's sarcoidosis, etc. These hepatic changes may represent an expression of defense mechanisms of the body.

The frequency of biochemical liver dysfunction in some systemic diseases has led to the postulate that hepatic abnormalities may be responsible for the disease process. Numerous studies have been conducted on the etiologic and therapeutic significance of hepatic dysfunction in gout, rheumatoid arthritis, allergic diseases, and dermatoses. Hepatic abnormalities cannot be incriminated as being causative in any of these conditions. Nevertheless,

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3

BIOCHEMICAL LIVER FUNCTION STUDIES AND SPECIAL LABORATORY PROCEDURES

LIVER function tests are valuable in the differential diagnosis of jaundice, furnish information on the functional reserve of the liver, determine the activity of the pathologic process, and permit recognition of subclinical liver disease In addition they serve as a guide for treatment and facilitate evaluation of response to therapy Liver function tests are most helpful when they are correlated with clinical and histologic findings. Serial sequential studies increase their usefulness.

Available tests measure excretory capacity and also assay the status of the metabolic processes Their results allow for more accurate evaluation of the ability of the liver to excrete and detoxify normal and artificial substances, determine the chemical constituents of the blood which may be altered, and directly or indirectly measure enzymatic activity and the pathologic materials produced in hepatic disease

More than 100 biochemical liver function tests have been proposed However, as pointed out by Hanger (1), only those which can be performed rapidly, inexpensively, and accurately, with minimal discomfort to the patient should be used in practice (Table 1)

58. Schatten, W. E., Desprez, J. D., and Holden, W. D. A bacteriologic study of portal vein blood in man. *A.M.A. Arch. Surg.* *71*:404, 1955.

59. Mateer, J. G., Baltz, J. I., Steele, H. H., Brouwer, S. W., and Calvert, J. B. Chronic subclinical impairment of the liver, early diagnosis and treatment. *J.A.M.A.* *133*:909, 1949.

than any single test or group of tests considered separately. This approach coupled with experience in individual diagnostic problems provides the practicing physician with an excellent background for intelligent selection of biochemical tests.

1. Jaundice of Undetermined Origin

The clinician is interested in deciding whether there is hemolytic, hepatic, or obstructive jaundice Excluding cases in which two or more of these mechanisms have been responsible for icterus, a correct differential diagnosis may be made in 80–90 per cent of patients on the basis of results from urine bile and urobilinogen, serum alkaline phosphatase, and protein flocculation tests (3) Uncomplicated hemolytic disease is characterized by increased urine urobilinogen, normal serum alkaline phosphatase, and negative flocculation tests. In most instances of hepatic jaundice, bile and urobilinogen are present in the urine, the alkaline phosphatase is normal or only slightly elevated, and the flocculation tests are positive In extrahepatic biliary obstruction and cholangiolar disease, there is bile and no urobilinogen in the urine, the serum alkaline phosphatase is elevated, and flocculation tests are negative

2 Viral Hepatitis

Selection of tests in viral hepatitis should be based on whether the patient is jaundiced Urine bile and urobilinogen, serum alkaline phosphatase, and protein flocculation tests are of chief value during the icteric phase Serum cholesterol esters, galactose tolerance, and hippuric acid tests provide confirmatory evidence of parenchymal disease Bromsulfalein excretion is the best single test in the nonjaundiced case, although urinary coproporphyrin or a flocculation test sometimes provides additional information (2b)

3 Nutritional Cirrhosis

Biochemical tests indicate the activity of the pathologic process, and evaluate functional reserve in patients with nutritional cirrhosis. Single observations are of little value An ideal battery of

Table 1 Liver Function Tests in Common Use

	Normal values	*Reference for method*
EXCRETORY TESTS		
One-minute serum bilirubin	0.1±0.05	(7)
Total serum bilirubin	0.6±0.25	(7)
Urine bile	Neg	(8)
Urine urobilinogen	1:20 (Wallace-Diamond)	(10)
	0.5–2.0 mg (24 hrs.)	(9)
Fecal stercobilinogen	100–250 mg	(11)
Bromsulfalein retention	Less than 5.0% in 45 min.	(14)
Serum alkaline phosphatase	5.0±2.0 (Bodansky U.)	(18)
Serum total cholesterol	160–240 mg%	(36)
METABOLIC TESTS		
Serum albumin	4.5–5.5 Gm%	(20)
Serum globulin	1.5–3.0 Gm%	(20)
Flocculation tests		
Cephalin cholesterol flocculation	0–1+	(21)
Thymol turbidity	8.0±2.0 U	(25)
Zinc sulfate turbidity	5.0±0.5 U	(23)
Prothrombin—vitamin K test	Correction of hypoprothrombinemia	(27)
Urine coproporphyrin	160–230 μg	(47)
Cholesterol esters	70–80% of total cholesterol	(36)
Glycogen storage test	35–50 mg%	(38)
Galactose tolerance	15±5.0 mg in 75 min.	(39)
Hippuric acid test	1.2±0.2 Gm	(2)
Glutamic oxalaceto transaminase	22.1±6.8 U	(45)

There is no specific biochemical pattern which is characteristic of a given type or severity of liver disease. Zieve and associates have applied statistical methods to analyze a group of liver function tests used on patients with hepatitis and cirrhosis (2). Their studies evaluate the interdependence among tests, attempt to determine which tests contribute independent information, and analyze the relative magnitude of the contribution of each test to the detection of liver disease. These authors found a combination of four significant tests was far more effective in diagnosis

Table 2 Illustrative Biochemical Liver Function Patterns

		EXCRETORY ABNORMALITIES			METABOLIC ABNORMALITIES				
Histologic diagnosis[a]	*No cases*	*BSP ret (%)*	*Elev s bil (%)*	*Elev alk. phos (%)*	*Elev total chol (%)*	*Abn prot part. (%)*	*Pos. ceph flocc (%)*	*Abn. chol. part (%)*	*Glycogen storage (%)*
Fatty liver	120	37	26	20	42	70	26	22	65
Mild viral hepatitis	35	100	95	10	20	7	90	65	90
Passive congestion	47	83	26	6	21	100	35	20	100
Biliary destruction	13		100	61	92	75	31	92	15
Metastatic cancer	67	48	27	77	6	100	24	42	18
Mild nutr fibrosis	22	60	50	31	45	40	31	45	15
Centrilobular fibrosis	9	11	44	33	44	100	44	22	20
Biliary fibrosis	17	100	100	94	82	87	41	64	25
Severe nutr. fibrosis	60	90	67	55	40	100	67	67	100
Postnecrotic scarring	10	100	80	20	60	100	60	30	100
"Cardiac" cirrhosis	9	100	66	22	11	100	33	33	100
Biliary cirrhosis	12	100	100	91	50	100	66	66	100

[a] Mixed pathology excluded

tests for long-term studies should include flocculation tests and enzyme studies to provide insight into the activity of the pathologic process, and serum protein partitions, serum cholesterol esters, hippuric acid synthesis, and bromsulfalein excretion to measure functional reserve.

4. Passive Congestion in Heart Failure

Biochemical liver function studies do not provide a clue to histopathology noted in heart failure (4). There is moderate retention of bromsulfalein and negative flocculation tests in patients with uncomplicated passive congestion. Serial study shows no alteration of biochemical reserve with mild fibrosis, but marked changes are noted with an intercurrent hepatitis, or development of centrilobular necrosis.

5. Metastatic Malignancy

The serum alkaline phosphatase is the best single test in suspected carcinomatous matastases to the liver An elevation of this enzyme in a nonjaundiced patient who has no bone disease is highly suggestive of metastatic malignancy or a granulomatous process involving the liver Sixty to 70 per cent of patients with hepatic metastases have an increase in serum alkaline phosphatase. Flocculation tests are usually negative; enzyme studies show increased transaminase and decreased cholinesterase activity. Other tests are of little additional value except in differentiating primary parenchymal disease.

Therapeutic Orientation

Biochemical tests are invaluable in objectively following the course of a patient with liver injury and his response to various therapeutic measures. This is illustrated by an analysis of the biochemical alterations which occur with progressive morphologic changes (Table 2) Fibroblastic transformation of the fatty liver is accompanied by increased retention of bromsulfalein and appearance of positive flocculation tests Biliary obstruction leading to fibrosis is associated with an increase of excretory dysfunction and protein and cholesterol abnormalities. Persistent

PATHOPHYSIOLOGY, TECHNIC, AND CLINICAL INTERPRETATION OF COMMONLY PERFORMED LIVER FUNCTION TESTS

Availability of a large number of liver function tests has made it necessary for each clinician and hospital group to select those tests which are simple to perform and provide maximum information. In the Jersey City Medical Center, a group of fifteen tests have been routinely obtained as a part of investigative studies. Some of these tests are of little value in diagnosis or treatment The following discussion will be concerned with a review of biochemical liver function tests believed to be of greatest value to the practicing physician Attention will be directed to bilirubin metabolism, bromsulfalein excretion, serum alkaline phosphatase, and selected studies of protein, cholesterol, and carbohydrate metabolism The value of enzyme studies, urinary coproporphyrin, and hippuric acid synthesis in patients with liver disease will also be reviewed

Bilirubin Metabolism

Serum bilirubin is a by-product of the catabolism of hemoglobin. Red blood cells break down to release hemoglobin which is converted into bilirubin-iron-globin Iron is split off this complex and bilirubin-globin is taken up by the liver The Küpffer and epithelial cells of the liver detach the globin molecule and secrete sodium bilirubinate into the bile Sodium bilirubinate is excreted through bile capillaries into intrahepatic and extrahepatic bile ducts which empty into the duodenum Small amounts of sodium bilirubinate are reabsorbed by the intestinal tract

As a result of bacterial action, sodium bilirubinate reaching the intestine is reduced to mesobilirubinogen, stercobilinogen and other chromogens, collectively referred to as urobilinogen Most of the urobilinogen is excreted with the feces, some is reabsorbed and taken up by the liver or re-excreted into the bile. Some of the reabsorbed urobilinogen escapes from the liver and appears in the urine (Fig 13A) The daily fecal and urine urobilinogen

alteration of excretory and metabolic functional abnormalities characterize development of fibrosis in patients with viral hepatitis and passive congestion. On the other hand, results of biochemical studies improve in patients with nutritional cirrhosis who receive optimum therapy. Likewise, there is improvement in biochemical reserve with surgical relief of biliary obstruction, subsidence of activity in viral hepatitis, and control of passive congestion of the liver in heart failure (5).

Choice of tests depends upon the etiology, stage, and activity of the hepatic disease. In acute reversible processes such as fatty liver and mild viral hepatitis, bromsulfalein excretion and flocculation tests are of greatest value in determining when healing has occurred. In chronic liver injury, study of bromsulfalein excretion, flocculation tests, and transaminase activity are helpful when there are no major symptoms and the clinician is interested in assaying activity in the parenchymal cells and connective tissue stroma. Repeated studies of bilirubin metabolism, serum prothrombin, and serum albumin and globulin are most valuable in patients who exhibit jaundice, bleeding tendencies, and fluid retention, respectively.

Interpretation of Tests

Numerous extrahepatic factors influence the results of liver function tests. Since none of the currently available biochemical studies is specific for hepatic functional reserve, each must be interpreted in conjunction with clinical findings. Technical errors alter laboratory results and contribute to difficulty in interpretation. It is necessary to modify accepted values for liver function tests in the newborn infant (6) and in patients with complicating diseases. After birth, bilirubin is slightly elevated, the globulin fraction of serum protein is higher, and the total serum cholesterol is lower. Chronic circulatory congestion, malnutrition, renal disease, thyroid dysfunction, and disorders of metabolism also exert considerable influence on the results of liver function tests.

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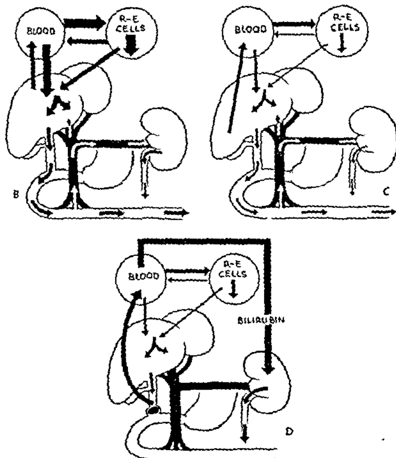


Fig. 13 (*contd*) B, Bilirubin metabolism with hemolysis C, bilirubin metabolism in hepatocellular disease, D, bilirubin metabolism with extrahepatic obstruction

of Hering and bile appears in the urine without having sodium bilirubinate reach the intestine

Extrahepatic biliary obstruction causes stasis of sodium bili-

serves as a measure of hemoglobin destruction One milligram of urobilinogen is derived from 23.9 mg of destroyed hemoglobin. Approximately 100–200 mg of urobilinogen appear in the feces, and 0 5–1.5 mg in the urine each day

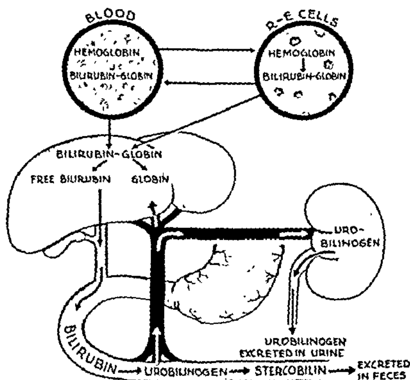


FIG 13 A. Normal bilirubin metabolism

Hemolysis accelerates the breakdown of red blood cells and *production of bilirubin-globin This causes an accumulation of* bilirubin-globin in the blood stream and is associated with an increased formation of sodium bilirubinate and increased excretion of fecal and urinary urobilinogen (Fig 13B)

Hepatocellular disease interferes with the transport of sodium bilirubinate. Regurgitation occurs from the bile capillaries into the perisinusoidal space and blood stream (Fig. 13C). Some of

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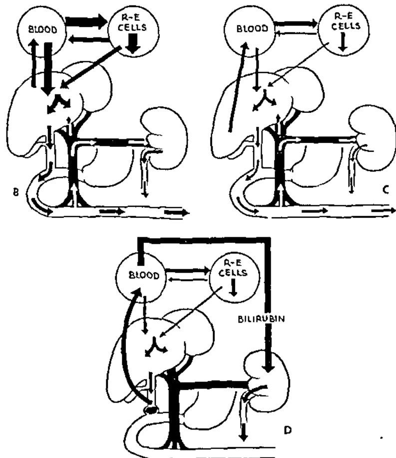


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rubinate in the bile capillaries. This causes hydrostatic dilatation and rupture of the bile capillaries, followed by leakage of bilirubin into the lymphatics of the liver. Bilirubin goes from the lymphatics into the blood stream. No bilirubin reaches the intestinal tract and bile appears in the urine without fecal or urinary urobilinogen (Fig. 13D) The serum bilirubin rises to a maximum level and fails to rise further due to a cessation of formation, increased degradation, or a combination of these mechanisms

Serum bilirubin is fractionated into that which is combined with protein (bilirubin-protein) and that which is free (sodium bilirubinate) by the rate of reaction with Ehrlich's diazo reagent. The color reaction resulting from a mixture of serum and the diazo reagent is called a direct reaction It has been attributed to bilirubin which is regurgitated from the biliary tree and consists of a sodium salt of bilirubin loosely bound to protein by absorption (prompt reacting bilirubin) Addition of alcohol to the serum reagent causes an intensification of this color reaction due to reaction with bilirubin which is firmly bound to protein by a valence bond (indirect bilirubin) (7)

Studies by Klatskin and his associates with filter paper electrophoresis suggest that the above concept is incorrect (7c). The hypothesis is advanced that reactability of bilirubin to diazotization depends upon solubility differences in selected media. Their investigations show serum bilirubin is largely bound to albumin and that differences in bilirubin-protein linkage are not responsible for the results of fractionation studies

Normal values

"One minute" bilirubin (Na bilirubinate) 0 01–0 5 mg 100 cc.
Indirect bilirubin (bilirubin-protein) 0 01–0 5 mg 100 cc.

Knowledge of the total serum bilirubin is valuable in confirming the clinical impression of jaundice and in serial following of icteric patients Fractionation of bilirubin has been used in the differential diagnosis of jaundice In our experience, this procedure is principally of value in the diagnosis of hemolytic jaundice, and is of limited help in distinguishing between biliary obstruction and hepatocellular disease. This is due to the fact that

the rate of diazotization is determined by both the concentration of bilirubin and chemical and physical factors in the serum Alteration of the ratio of direct to indirect bilirubin is pathologic, although the total value may be normal.

Urine Bile

Numerous tests are available for detection of biluria In the *foam test*, the urine is shaken and the resulting foam observed for a yellow color characteristic of bile The *methylene blue test* consists of adding 1 per cent methylene blue to 5 ml of urine drop by drop, and if more than six drops are required to establish a blue color, the reaction is read as being positive for bile The *iodine ring* test consists of overlaying 5 ml of urine with saturated solution of iodine, and if a green ring appears at the interface of these solutions, bile is present The *Harrison spot test* (8) is the preferable test Five milliliters of urine is added to 5 ml of 10 per cent barium chloride to precipitate bilirubin in this test The precipitate is filtered and 2–3 drops of Fouchet's reagent (trichloracetic acid and ferric chloride) is added to it Bilirubin is oxidized by Fouchet's reagent to produce a green color, the intensity of which indicates the concentration of bile present

The appearance of bile in the urine is abnormal and is seen only in patients with primary liver disease or obstructive jaundice Daily urine bile studies are of value in following the course of jaundice due to acute parenchymal disease

Urine and Fecal Urobilinogen and Urobilin

Ehrlich's aldehyde reagent reacts with urobilinogen to form a red color This colorimetric reaction may be used on the urine or feces to estimate the amount of urobilinogen present The semiquantitative method for urine studies has proven useful in studies of liver disease (9) In this test, a two-hour specimen is collected between 12 00 noon and 2 00 P M Normally 0 3–1 0 Ehrlich units of urobilinogen is excreted in a two-hour period A simple, less refined semiquantitative test for urobilinogen is the Wallace-Diamond method (10) This test is performed with urine diluted

from 1:10–1:100. Normally, urobilinogen is present in urine up to 1:20.

Urobilin is an oxidation product of urobilinogen. In normal urine, the relative amounts of urobilinogen and urobilin vary depending upon whether there is an over-all tendency for reduction or oxidation. Urobilin has the same clinical significance as urobilinogen. It is normally present in the urine in health, and its concentration increases with stagnation. Urobilin is detected by a green fluorescence which is proportional to its concentration when 4 ml. of urine are added to 4 ml. of saturated alcoholic solution of zinc acetate and a filtrate of the resulting mixture viewed above a strong light.

The *Watson test* (11) permits rapid and accurate measure of fecal urobilinogen and urobilin. These substances are extracted from the stool with an alcoholic solution of zinc acetate. Ehrlich's aldehyde reagent is added to detect urobilinogen and sodium acetate to detect urobilin. Approximately 2 Gm. of fresh stool are desirable to estimate fecal urobilinogen, any stool may be tested for its urobilin content.

Excretion of urobilinogen is increased with hemolytic disease. A decrease occurs with obstruction to bile outflow, diarrhea, and use of antibiotics which interfere with conversion of bile to urobilinogen in the intestine. The newborn infant has little fecal or urine urobilinogen because of the rapid passage of material through the lower gut. Renal dysfunction may interfere with urinary pigment excretion.

Urobilinogen studies are helpful in recognizing and following the course of hemolytic disease and primary hepatic disease. Considerable reliance can be put on these studies if care is taken to remove bile. The clinician has to be certain that the test is done before there is oxidation of urobilinogen to urobilin. Urobilin should be studied concomitantly when testing is delayed. The presence of normal or increased urine urobilinogen eliminates the possibility of complete biliary obstruction. A diagnosis of obstructive jaundice is suggested when urobilinogen is persistently absent from the feces and urine. However, urine urobilinogen may be present in patients with biliary obstruction and an ascending

cholangitis as bacterial action in the biliary tree causes degradation of sodium bilirubinate to urobilinogen

Bromsulfalein Excretion

An intact liver is necessary for the removal of a large number of dyes from the blood stream Study of the rate of removal provides an index to hepatic functional capacity Bromsulfalein is the least toxic of the available dyes

Bromsulfalein is rapidly distributed throughout the body when it is introduced into the systemic circulation. A variable amount is removed by tissues of extrahepatic organs including the diaphragm, heart, lung, kidney, spleen, and intestine (12) Theoretically the loss is not significant It has been suggested that uptake is a physicochemical process wherein bromsulfalein is bound to intracellular proteins (12) Approximately 98 per cent of the bromsulfalein initially reaches the liver, the rate depending on the circulation The dye is taken from the sinusoids by the liver and reticuloendothelial cells. It is then excreted into the bile Fifty to 85 per cent of injected bromsulfalein appears in the bile in one hour, and 65–90 per cent in two hours. The remaining dye is temporarily stored in the reticuloendothelial system

Delayed excretion of bromsulfalein may reflect an abnormality of the systemic or hepatic circulation, liver cell dysfunction, or reticuloendothelial abnormalities It is removed from the blood more completely in the postabsorptive than in the fasting state (13) Hepatic blood flow may be estimated with bromsulfalein using clearance technics with comparison being made between dye concentration in systemic venous blood and hepatic venous blood obtained by hepatic vein catheterization

Technic for performing the bromsulfalein test is better standardized than any other test for biochemical liver function study Dosage calculation and time should be rigidly adhered to for uniformity of results (14) The preferable procedure is to inject 5 mg Kg of bromsulfalein in the fasting state over a period of one minute, avoiding extravasation Forty-five minutes after completing the injection, 5 ml of blood should be drawn from the opposite arm in a dry syringe and the amount of dye in the serum

determined by colorimetric methods Retention of 5 per cent or more of the dye at the end of 45 minutes is considered abnormal.

Abnormal retention of bromsulfalein occurs independently of the functional capacity of the liver in congestive heart failure, shock, venous shunts that by-pass the liver, and other pathologic states associated with a decreased hepatic blood flow. Disease of the biliary or reticuloendothelial systems also alters clearance. Abnormal dye retention is attributed to dysfunction of parenchymal liver cells in the absence of these states.

The bromsulfalein test is of little value in establishing a specific diagnosis. Where used on chronic alcoholics with normal liver, focal inflammation, fatty liver, and nutritional cirrhosis the results are similar (15) Bromsulfalein excretion is useful in the emergency differential diagnosis of massive hemorrhage from esophageal varices and peptic ulcer Shock in itself produces abnormal bromsulfalein clearance However, retention of more than 30 per cent of the dye is suggestive of primary liver disease.

The bromsulfalein test is of chief value in determining when acute liver disease is healed In viral hepatitis dye clearance helps to establish an optimum time for ambulation of the patient. Bromsulfalein retention shows evidence of continued liver damage and constitutes an early sign of reactivation of hepatitis Although this test may be performed in the icteric patient, using appropriate filters to eliminate bilirubin effect, it provides little information of clinical value in the presence of jaundice.

Alkaline Phosphatase

Alkaline phosphatase is present in blood, serum, bone, liver, kidney, intestine, mammary gland, spleen, lung, adrenal cortex, and seminiferous tubules Plasma levels are low at birth, rise rapidly to a maximum during the first month of life, and remain high during the active growth period This enzyme is normally excreted in the bile

Elevation of serum alkaline phosphatase occurs when its production is increased or excretion interfered with. Increased production occurs with osteoblastic activity during normal growth and in diseases such as rickets, hyperparathyroidism, Paget's

disease, and bone tumors. An elevated serum alkaline phosphatase is frequently seen in biliary obstruction and has been attributed to an excretory defect (16). The alkaline phosphatase is probably maintained at normal levels by a different excretory mechanism from serum bilirubin (1). As an obstructive process develops, a rise frequently appears before hyperbilirubinemia. It has been suggested that regeneration of liver tissue in biliary obstruction and of tumor cells in neoplastic diseases may stimulate production of alkaline phosphatase (17).

Serum alkaline phosphatase may be determined by the Bodansky or King-Armstrong methods (18). Approximately 5 ml of serum are needed for the chemical determination. Care must be taken in drawing the blood to avoid hemolysis. The alkaline phosphatase is normally between 1.0 and 4.0 units by the Bodansky method, and between 2.0 and 13.0 units by the King-Armstrong method.

This test is valuable in the diagnosis of biliary obstruction and metastatic malignancy (Fig. 14). In the icteric patient, an elevated alkaline phosphatase suggests biliary obstruction, without jaundice, it suggests metastatic malignancy. Enzyme levels of more than 15 Bodansky units are obtained in 90 per cent of patients with extrahepatic obstructive jaundice. The alkaline phosphatase is elevated in 60 per cent of patients with metastatic carcinoma to the liver. Cholangiolitic hepatitis and cirrhosis, of viral or toxic origin, are characterized by a high level of this enzyme. Patients with uncomplicated fatty liver, hepatitis, passive congestion, and nutritional cirrhosis have a normal or only slightly elevated serum alkaline phosphatase.

STUDIES OF PROTEIN METABOLISM

The liver is responsible for the synthesis of albumin, fibrinogen, and prothrombin, participates in the manufacture of globulin, and is the site of deamination, transamination, and production of urea. Nitrogen is stored in this organ, and the specific dynamic action of protein largely depends upon metabolic processes which occur in the liver. Clinical measures of these functions are im-

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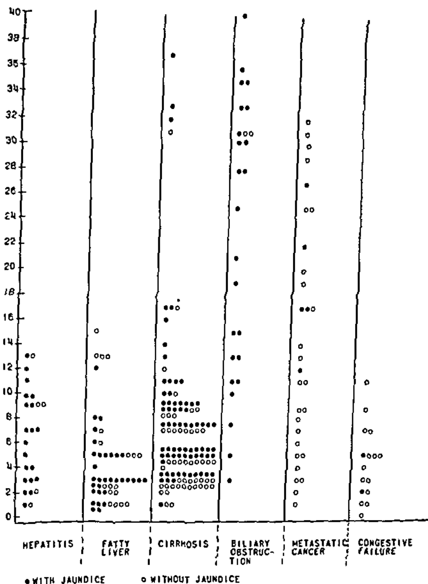


FIG 14 Serum alkaline phosphatase in hepatic disease

portant in assaying reserve of the liver. In addition, they provide useful information for therapy and diagnosis Knowledge of the serum albumin level is important in patients with fluid retention. Tests which reflect an elevation of globulin provide an index to the activity of a pathologic process, and the prothrombin time is essential in study of patients with hemorrhagic tendencies

Serum Albumin and Globulin

Two methods are available in the clinical laboratory for separating plasma protein: differential precipitation in neutral salt solutions, and electrophoretic analysis Chemical determination by salting-out procedures, and separation of proteins on the basis of their migration in an electric field yield divergent results (19) Chemical study provides an adequate evaluation for clinical purposes (20) By this method, the total serum protein is 6 8–7.5 Gm/100 cc., of which 3 0–5 0 Gm/100 cc. is represented by albumin and 1 3–3 3 Gm/100 cc by globulin. When possible, it is desirable to estimate the total circulating protein by simultaneously determining the plasma volume and serum protein concentration This type of study corrects for errors made by plasma volume alterations. A paper electrophoresis is simpler than free electrophoresis and is more readily adaptable to clinical work Typical curves which help in diagnosis are seen in both types of electrophoretic analysis (Fig 15) Serum in normal persons using electrophoretic separation techniques shows approximately 55 per cent albumin and 45 per cent globulin, with 5 3 per cent α_1 globulin, 8 7 per cent α_2 globulin 13 4 per cent β globulin, 11 0 per cent γ globulin and 6 5 per cent fibrinogen

Hypoalbuminemia which reflects a decrease in tissue albumin is usually present in severe or chronic liver disease Acute liver injury does not significantly alter the serum albumin Low serum albumin in liver disease is due to a decrease in the production of albumin or excessive loss of albumin in ascitic fluid. Studies of iodinated albumin show that approximately 40 per cent of total body albumin is in the plasma, and the remainder is in the lymph interstitial space, and possibly intracellular space (21). One half of the total iodinated albumin in the serum leaves the

vascular compartment every 15 hours and is replaced by albumin returning from extracellular areas. The normal liver synthesizes approximately 18.0 Gm. of albumin per day to maintain body protein stores, and this amount increases considerably with threatened body depletion (22). Unlike healthy subjects, patients with hepatic cirrhosis are frequently unable to synthesize more than

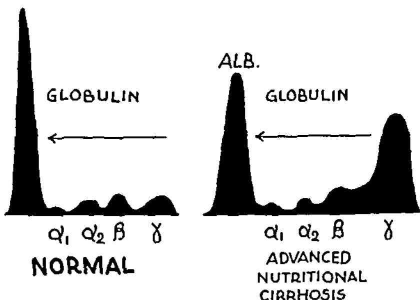


Fig. 15. Electrophoretic protein pattern in a patient with severe liver disease compared with a normal pattern.

9–10 Gm. of albumin daily, although they have no alteration in rate of albumin exchange or amount of degradation. The inability of the liver to increase production of albumin to replace loss into accumulating ascitic fluid causes a lowering of tissue and serum albumin.

Serum globulin is characteristically increased in liver disease. Electrophoretic studies show high values for alpha, beta and gamma globulins. Elevation of serum globulin does not, in itself, indicate liver dysfunction as numerous conditions are accompanied

by hyperglobulinemia. The cause of the hyperglobulinemia in liver disease remains unknown Studies with I^{131} tagged gamma globulin demonstrate an increased rate of production and accelerated degradation of this protein in patients with liver disease who have hyperglobulinemia (21). Patients with chronic liver disease have from 2–10 times a normal concentration of globulin Hyperglobulinemia has been attributed to stimulation of the reticuloendothelial system as a part of an immunologic mechanism There is some evidence to suggest plasma cells, which are increased in liver disease, may be the source of globulin

Flocculation Tests

More than 20 liver function tests have been devised to indicate reactions which occur with qualitative and quantitative abnormalities in the serum albumin or globulin The most popular are the zinc sulfate turbidity, cephalin cholesterol flocculation, and thymol turbidity tests A combination of these tests improves diagnostic perspective since their results depend on different physicochemical changes in the patient

The zinc sulfate turbidity test furnishes a reliable estimate of gamma globulin. Dilution of serum containing a high gamma globulin level with a properly prepared solution of zinc sulfate produces a turbid precipitate (23) Elevated zinc turbidity is seen in nutritional cirrhosis, cholangiolitic cirrhosis, and chronic viral hepatitis This test is of special value in recognizing hepatocellular jaundice in the newborn where other functional tests are often misleading (6)

The cephalin flocculation test consists of mixing serum with an especially prepared cephalin cholesterol emulsion and observing the degree of precipitation in 24 and 48 hours (24) A positive test depends upon the absence of stabilizing factors in the serum which normally prevent gamma globulin from producing this reaction The stabilizing material consists of labile, lipid rich constituents of the albumin-α-1-globulin fraction of plasma proteins (1) This material disappears from the serum within 48 hours after acute hepatocellular damage and does not return until healing has begun (1) The cephalin flocculation is correlated

with the activity of liver disease as reflected in clinical stigmas and histologic alterations This reaction is useful in studies of the jaundiced patient, in recognizing subclinical liver injury, in following the course of active hepatic disease, and in determining the need for continued therapy Extrahepatic biliary obstruction and cholangiolitic hepatitis are accompanied by a negative cephalin flocculation unless there is secondary infection. In contrast, 80 per cent of the patients with icterus due to viral hepatitis, active nutritional cirrhosis, and other parenchymal diseases have a positive reaction Anicteric viral hepatitis and other subclinical hepatic diseases may be recognized by using this test. Serial therapeutic follow-up in acute liver injury with the cephalin flocculation test theoretically provides information on the pathologic process and aids in deciding therapy

A positive cephalin flocculation reaction in nonhepatic diseases limits the over-all diagnostic value of this test. It is common in diseases involving the reticuloendothelial system such as infectious mononucleosis, malaria, and lupus erythematosus. False-positive reactions represent another pitfall commonly seen with this test The sensitivity of the test varies with the age of the cephalin, the amount of light, and presence of contaminants. Normal controls must be evaluated periodically to determine accuracy of results of the test

A positive thymol turbidity reaction depends upon an alteration in serum albumin, elevation of beta and alpha globulin, and an increase in lipids or lipoproteins. This test performed by adding a mixture of thymol, barbital, and sodium barbital to the test serum (25) serves as a supplement to the zinc sulfate turbidity and cephalin flocculation tests. It is useful in following the progress of recovery in acute liver disease, and in differentiating intrahepatic and extrahepatic jaundice The thymol turbidity usually becomes positive later than the cephalin flocculation and tends to remain positive in the healing phases of hepatitis after the cephalin flocculation has returned to normal. Use of a thymol reagent buffered at pH 7 55 is associated with a higher incidence of positive responses than with the reagent buffered at pH 7 8 Hyperlipemia causes a positive reaction and decreases the selectivity of the test in liver disease (26).

Prothrombin Tests

The liver is responsible for the manufacture of components of the prothrombin complex, the thromboplastin complex, and fibrinogen, all of which are necessary for blood clotting. Plasma prothrombin time measures deficiencies of the prothrombin complex, the prothrombin consumption test provides a measure of the thromboplastinogen complex, and plasma fibrinogen may be determined directly A prothrombin deficiency is frequently present in liver disease and is due to a lack of vitamin K, or liver cell injury which interferes with the manufacture of prothrombin, or the production of the labile factor An abnormal prothrombin consumption time results from a platelet deficiency, thrombasthenia, or deficiency of accelerator substances in the plasma (27)

The one-stage plasma prothrombin time should be followed by a repeat study within 24 hours after giving 72 mg of vitamin K ✓ if results are abnormal Prothrombin deficiency due to extrahepatic abnormalities can usually be corrected with vitamin K Patients with primary liver disease do not respond well to vitamin K unless there is a coexisting vitamin K deficiency This test is helpful in the differential diagnosis of jaundice Patients with obstructive jaundice have a return of prothrombin time to normal after vitamin K therapy, those with hepatic jaundice have little alteration of prothrombin time when vitamin K is given Hypoprothrombinemia which is refractory to vitamin K is caused by a deficiency of prothrombin or labile factor, or the presence of an inhibitor or fibrinopenia It is possible to differentiate between a deficiency of prothrombin and labile factor by adding 10 per cent aluminum hydroxide treated plasma and performing the one-stage clotting time Aluminum hydroxide will shorten the one-stage clotting time when the labile factor is deficient The presence of an inhibitor or fibrinopenia should be suspected if a mixture of equal parts of the patient's and normal plasma has a one-stage clotting time of more than two seconds longer than normal plasma (28)

A simplified method using commercially prepared reagents makes the serum prothrombin consumption test a practical pro-

cedure (29) In this test, serum is separated from clotted blood, mixed with a freshly prepared thromboplastin-fibrinogen solution, and the time for a clot to form is determined. This time is normally over 30 seconds. The range between 20 and 30 seconds is doubtful, shorter than 20 seconds is abnormal. Delay in performing the outlined steps of the test, or other alterations in time or procedure causes considerable variation in results.

Studies of Protein Deamination and Urea Synthesis

The liver and kidneys are responsible for deamination of proteins. The amino group is split off as ammonia and contributes to the formation of urea. The deaminated protein is resynthesized into an amino acid, converted to glucose or a fatty acid, or oxidized to carbon dioxide and water Ammonium formed in the intestines by the action of bacteria or nitrogenous substances enters the portal circulation and is converted by the liver into urea Estimation of total amino acid nitrogen in the blood and urine, blood ammonium and blood urea furnishes insight into these mechanisms.

The normal amino acid level of the serum is 4–8 mg/100 cc. Efficiency of amino acid metabolism is decreased with severe liver damage and the serum concentration sometimes rises to a level of 200 mg 100 cc The normal urine amino acid which averages 20 mg 100 cc in health also increases markedly with acute hepatic insufficiency

Paper chromatographic studies of free amino acids in the plasma of patients in hepatic coma demonstrated an increase in glutamic acid, glutamine, tyrosine, cystine, and methionine (30). These findings were not consistent The majority of patients had an increase in plasma concentration of one or more amino acids.

Blood ammonium level becomes elevated when portal circulation by-passes the liver in an Eck fistula, or hepatic blood flow is reduced in chronic hepatic disease (31) In chronic liver disease it is reduced by fasting and ingestion of carbohydrates, it is increased with protein feeding, high meat intake, and ingestion of ammonium chloride and other ammonium salts. The major value of this determination is in diagnostic study of hepatic coma where

there is an elevation of the ammonium level Sensorial changes may precede its rise. Its chief limitation is the lack of standardization of current chemical methods for performing the test (32)

In marked hepatic disease the formation of blood urea is decreased. This may sometimes be a helpful prognostic sign However, in most instances it is not of value for there may be associated renal dysfunction which also causes an increase in blood urea

STUDIES FOR FAT METABOLISM

The outstanding change in plasma lipids in liver disease is an alteration of the ratio of free to total cholesterol (33) The liver is responsible for the cholesterol and cholesterol ester content of the plasma It manufactures and discharges cholesterol into the plasma and later removes and destroys it or converts it into cholic acid Cholesterol is also synthesized by the intestinal mucosa, adrenal cortex, walls of arteries, and other tissues Acetate is its major precursor

Maintenance of serum cholesterol levels depends on the binding properties of alpha and beta globulin, and the absorptive capacity of plasma protein Cholic acid, produced by the liver, appears to control cholesterol levels indirectly by changing the absorptive capacity of plasma protein or by increasing the alpha and beta globulin content of the serum Correlation of total cholesterol with bile acids shows serum cholesterol to vary directly with the level of bile acids (34) There is a rapid turnover of plasma cholesterol, 50 per cent being replaced daily Hypocholesterolemia occurs when there is a reduction in synthesis of cholesterol, hypercholesterolemia develops when the rate of destruction of cholesterol is decreased

The Bloor technic (35) for chemical estimation of serum cholesterol and cholesterol esters is suitable for detection of gross abnormalities More precise information is provided by the Schoenheimer-Sperry method (36) and, if available, this is the procedure of choice In the presence of esterifying enzymes, free cholesterol of the serum tends to decrease, and cholesterol esters increase (37) In liver disease cholesterol esterifying enzymes may

be diminished and this has been used as the basis for a test of liver function. One can assume there is a deficiency of the esterifying enzyme if free cholesterol does not decrease at least 30 per cent in 24 hours at 37°C.

The total cholesterol may fall to levels of less than 100 mg./100 cc. in terminal liver disease. A similar reduction has been noted in marked inanition, anemia, thyrotoxicosis, and during the terminal phase of many unrelated chronic illnesses. Uncomplicated extrahepatic obstructive jaundice is accompanied by an elevated serum cholesterol. Primary disease of the cholangioles also causes a marked elevation sometimes as high as 2500 mg./100 cc. The serum cholesterol is of limited value in diagnostic appraisal of hepatic status in patients with familial hypercholesterolemia, nephrosis, diabetes, pregnancy, and hypothyroidism.

In liver disease estimation of serum cholesterol esters provides more information than the total cholesterol. A decrease in cholesterol esters is observed in severe hepatic insufficiency. However, similar degrees of interference with cholesterol esterification occur in patients with nonhepatic disease and it is necessary to correlate test results with clinical findings.

TESTS FOR CARBOHYDRATE METABOLISM

Dysfunction of the liver may lead to impaired glycogen storage, decreased galactose, levulose or lactic acid tolerance, abnormal glucose tolerance, hypoglycemia, or hyperglycemia. We have found carbohydrate tests to be of value where correlated with other clinical data. The major value of a measure of glycogen storage capacity in liver disease appears to be its use as a guide to therapy. The intravenous galactose tolerance test is useful in the study of the jaundiced patient. The intravenous glucose tolerance test, performed with simultaneous inorganic phosphorous studies, is helpful in the study of patients with blood sugar changes associated with liver disease.

The glycogen storage test may be performed with either epinephrine or glucagon, both of which increase glycogenolysis. One one-hundredth cubic centimeter of 1:1000 epinephrine/Kg. of body weight given intramuscularly, or 0.01 cc. glucagon/Kg.

of body weight intravenously will cause a rise in blood sugar of approximately 40 mg/100 cc during the course of one hour. Patients with starvation, glycogen storage disease, or galactosemia have little rise in blood sugar Uncontrolled diabetes is associated with a variable increase of sugar, in some instances being low, and in others ranging as high as 170 mg/100 cc Fatty liver, decompensated nutritional cirrhosis, acute viral hepatitis, and passive congestion of the liver due to congestive heart failure are associated with a decrease in response, proportional to the degree of liver injury Patients with uncomplicated biliary obstruction or patchy neoplastic infiltration of the liver have normal responses (Table 3). There is a correlation between the clinical severity of

Table 3 Glycogen Storage Variants in Disease

Disease	*No of studies*	*Maximal rise of blood sugar (mg/100 cc)* *Range*	*Average*
Normal	20	35–50	40
Uncomplicated metastatic carcinoma	12	25–46	35
Hepatic congestion	21	14–26	18
Diabetes mellitus uncontrolled	18	20–170	70
Uncomplicated obstructive jaundice	15	35–55	42
Severe acute liver disease	21	4–20	11
Severe chronic liver disease	23	8–25	16

the liver disease and the glycogen storage test, and between other biochemical functions and this test (38) Results of the epinephrine test are altered by variation of epinephrine to norepinephrine content of commercial solutions, absorption, and state of circulation Both the epinephrine and glucagon tests are affected by previous diet and muscular activity Hyperglycemia resulting from glucagon also depends upon the rate of peripheral glucose assimilation This action is minimized when a small amount of epinephrine is administered before giving glucagon It is recommended that a combination of epinephrine and glucagon be used in clinical practice (38)

The galactose tolerance test has not been widely used because

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when cholinesterase hydrolyzes acetylcholine under controlled conditions (43) By this method, normal cholinesterase values are 0 66±0 22 units The serum cholinesterase is usually decreased when the serum albumin level is low. Low values of this enzyme have been found in patients with acute parenchymatous liver disease and metastatic carcinoma

Serum glutamic oxalacetic transaminase is elevated in the early stages of acute liver cell injury. This finding is useful in diagnosis and in following the course of parenchymatous disease It is high in toxic and infectious hepatitis, moderately elevated in obstructive jaundice and liver metastases, and variable in cirrhosis Its increase may indicate active liver cell destruction The test is based on increase in a specific tissue enzyme which is distributed in animal tissues with greatest concentration in the heart muscle, skeletal muscle, brain, liver, and kidney in decreasing order. It is concerned with the transfer of an amino nitrogen of aspartic acid [illegible]

Tissue injury results in a decrease in glutamic oxalacetic transaminase activity and is associated with a relatively proportional increase in the activity of the serum Practical usefulness of this test has been demonstrated in diagnostic study of patients with suspected myocardial infarction and hepatic disease (45)

Hippuric Acid Test

Benzoic acid is converted in the body to hippuric acid and measures of the rapidity and completeness of this reaction provides a valuable test of liver function A normal subject given 1 77 Gm of sodium benzoate intravenously excretes 0 7–0 95 Gm of hippuric acid in the urine during the first hour This test depends upon the presence of coenzyme A, adenosine triphosphate, a specific enzyme "glycine Nacylase" (46), and glycine in addition to benzoic acid Also adequate oxygen, an intact circulation, and normal renal tubular function are necessary if a measure of benzoic acid conjugation is to be used as an assay of hepatic reserve.

of technical difficulties with the intravenous test and inaccuracy of oral methods. The liver is the key organ in the metabolism of galactose and through its activity galactose is removed from the blood. Serial determinations show a progressive decrease of serum galactose following its infusion in healthy subjects. Liver dysfunction decreases the capacity to convert galactose to glycogen, and galactose concentrations remain high for longer periods (39). In normal subjects, *no galactose is found in the blood stream at the* end of 75 minutes after infusing 0.5 Gm. of galactose/Kg of body weight intravenously over a 2–3 minute period.

Glucose tolerance tests are important in studies of liver disease associated with hyperglycemia and hypoglycemia. The normal curve depends on the integrity of the liver, a quantitative relationship existing between the amount of functioning liver parenchyma and tolerance to glucose. The test with simultaneous inorganic phosphorous determinations may be useful in differentiating the diabetic-like curve seen in liver disease from that due to diabetes mellitus (40). With infusion of glucose in healthy subjects, serum phosphorus decreases due to its use in the phosphorylating mechanism. In diabetes mellitus, where phosphorylation does not proceed normally, there is little or no reduction in phosphorous levels with infusion of glucose. Patients with liver disease respond similarly to healthy subjects. With fasting hyperglycemia associated with liver disease, there has been a variable response which prevents the use of this test in deciding the etiologic relationship of the hyperglycemia and liver disease (41). Cortisone given to patients with liver disease who have normal carbohydrate metabolism does not cause an abnormal tolerance curve. However, the hyperglycemic response in patients with latent pancreatic diabetes as well as those with hepatogenic diabetes is accentuated by cortisone (42).

ENZYME STUDIES

Serum cholinesterase provides an index to the efficiency of hepatocellular protein synthesis. It may be determined by a colorimetric method which measures the acetic acid liberated

sure or hepatic vein wedge pressure may give important indirect information on the degree of portal hypertension.

Radiography of the Liver

Roentgenograms of the liver are useful in helping to evaluate abnormal resonance over the liver They also provide objective information on liver size and reveal unsuspected liver opacities By this method it can be determined if the colon is between the liver and chest wall Liver enlargement is evident on x-ray when obesity and ascites are not present X-ray study is valuable in establishing the degree of hepatomegaly Rarely, roentgenograms show opacities in the substance of the liver including hemosiderin, hepatic calculi, and calcium deposits in a hemangioma, amoebic abscess, or echinococcus cyst

Cholecystography

Cholecystography is important in patients with liver disease who have signs and symptoms suggestive of acute cholecystitis or biliary colic It is not associated with untoward effects We have obtained it routinely in older patients with chronic liver disease (48) Telepaque, a tri-iodinated substance, has been used for oral cholecystography, Cholografin, which contains four iodine molecules, has been used for intravenous studies Theoretically, only 40-60 per cent of ingested Telepaque is excreted by the liver, the rest appearing in the urine Eighty to 90 per cent of injected Cholografin goes to the liver for excretion Relatively high concentrations of Cholografin appear in the biliary ducts within 20-25 minutes This characteristic permits visualization of the biliary passages in the absence of gallbladder concentrating power

In 75 patients with nutritional cirrhosis, gallbladder visualization was good in 22 (30 per cent), poor in 25 (33 per cent), and absent in 28 (37 per cent) Unsuspected gallstones were demonstrated in 9 (12 per cent) patients The degree of visualization of the gallbladder in nutritional cirrhosis without jaundice is related to the severity of the liver disease High levels of bromsulfalein retention, 3 plus to 4 plus cephalin flocculation, and marked fibrosis on biopsy are associated with nonvisualization although jaundice is absent Hepatic therapy leads to improved gallbladder

URINARY COPROPORPHYRIN

Liver disease is associated with an increase in the total urinary coproporphyrin above the upper limit of normal (100 μg/24-hour urine sample). This finding is valuable in recognizing residual liver damage in patients with viral hepatitis and other acute hepatocellular disease. There may be persistent elevation after bilirubin, cephalin flocculation, and bromsulfalein have become normal (47). Isomer analysis shows that the increase is due mainly to the Type I isomer. There may also be an increase in Type III isomer in patients with biliary obstruction due to cancer of the pancreas, bile ducts or liver.

SPECIAL LABORATORY PROCEDURES

Dysfunction of multiple physiologic systems in patients with chronic hepatic disease makes it necessary to perform a large number of laboratory procedures not related to the liver per se. A complete discussion of technical procedures which may be required in evaluating patients with liver disease would involve most of the available clinical laboratory methods. The reader is referred to other texts for detailed descriptions of these methods. Recommended studies have proven largely of academic value in many instances, however, they sometimes provide information essential for proper therapy. The patient with decompensated nutritional cirrhosis accompanied by splenomegaly, hemolytic anemia, and ascites is illustrative. A combination of clinical, biochemical, and histologic studies furnishes general therapeutic orientation. Additional information relative to the desirability of performing a splenorenal shunt to remove an overactive spleen and reduce portal hypertension when medical therapy fails may be provided by specialized technics such as radioactive chromium studies, and transesophageal venous pressure study or hepatic vein catheterization. Study of Cr^{51} tagged erythrocytes in conjunction with urinary and fecal urobilinogen assays allows the clinician to evaluate red blood cell survival, and assess the role of an enlarged spleen in hemolysis. Estimation of esophageal varix pres-

in samples of tissue from the metastases and surrounding normal tissue in 29 patients by Stirrett and associates (50) revealed increased radioactivity in the metastases varying from 13-64 per

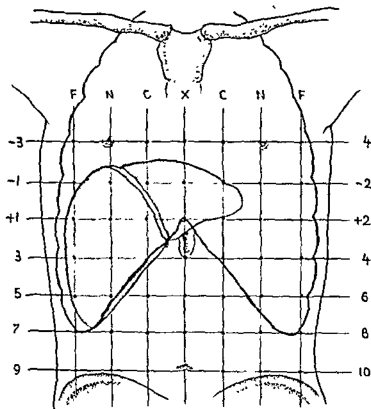


Fig 16 Abdominal sketch used in plotting radioiodine pick up in metastatic carcinoma to the liver (Modified with permission, Stirrett, Yuhl, and Libby Surg, Gynec and Obst 96 210, 1953)

cent However, tissue from the primary neoplasm often did not show more radioactivity than adjacent normal tissue The extent of hepatic metastases rather than the histologic type determines the degree of increased radioactivity (50) When metastatic lesions are more than 2 cm in diameter the uptake of iodinated

visualization. Ninety per cent of patients with jaundice due to decompensated nutritional cirrhosis have nonvisualization of the gallbladder. On the other hand, elevated bilirubin to 10 mg/100 cc. in acute hepatitis does *not interfere* with cholecystography.

Percutaneous Splenography

[illegible] other contrast media into the spleen [illegible] in many instances [illegible] attern of the portahepatican. It provides impo[illegible] ior to surgical procedures and aids in recognition of splenic vein thrombosis, portal vein occlusion, and vascular anomalies. Using a #22 gauge needle and 20 cc. of the contrast medium injected steadily over a four-second period, x-rays obtained between 4 and 10 seconds usually demonstrate the vascular pattern (49). A manometric device attached to the needle permits an indirect measure of portal pressure.

Radioactive Tracer Studies in Localizing Discreet Lesions of the Liver

Radio-iodine uptake is increased in areas of metastatic carcinoma of the liver, and this fact has been used to recognize neoplastic lesions preoperatively (50). Comparison of the activity

Table 4. Control Values in Radioisotope Scans. Control Ranges for Average Sized Individual in Radioactive Survey Technic for Recognition of Localized Hepatic Lesions.*

	A	B	C	D	E	F	G
1	33–53	39–93	75–117	109–149	92–146	55–103	39–57
2	28–68	39–99	68–110	93–141	84–138	54–94	37–55
3	24–82	57–97	76–104	Xiphoid	78–108	53–91	33–67
4	29–65	53–81	64–92	77–101	65–107	48–90	32–60
5	16–58	38–72	53–81	60–90	56–90	48–78	31–53
6	22–56	41–60	48–78	56–86	48–76	44–66	31–47

Suitable controls must be established in each radioisotope laboratory and should include separate studies for patients with small, average, and large body builds.

* With permission, Sturrett, Yuhl and Libby, Surg., Gynec. and Obst., 96:210, 1953.

normal liver biopsy in the presence of marked increased radioactivity in a localized area suggests the focal lesions are beyond the reach of the needle. Radioisotope survey technics and needle biopsy should be combined with clinical evaluation and biochemical study to obtain maximum information This method is of greatest value in the diagnosis of metastatic cancer to the liver Less frequently, a positive biopsy may be obtained in a granulomatous lesion by this technic. Further refinement of technics may increase the ability to detect localized lesions (51)

Hepatic Vein Catheterization

The technic of cardiac catheterization has been extended to introduce a catheter into the hepatic veins for the purpose of measuring pressures and sampling blood from these vessels. This provides considerable information of academic and practical importance on the influence of varying drugs and pathologic states on hepatic blood flow, carbohydrate metabolism, ammonium metabolism, and hepatic venous pressure (52) Thus, curtailment of physical activity in chronic liver disease is based partly on the decrease in hepatic blood flow, increased oxygen extraction, and increased A-V difference which is characteristic of hepatic cirrhosis.

The demonstration that an elevated portal vein pressure is accompanied by a corresponding increase of wedged hepatic vein pressure makes this an important study in clinical practice (53) Portal hypertension may be predicted from the finding of an elevated pressure when a cardiac catheter is wedged into a peripheral hepatic venule Wedged hepatic venous pressure reflects the results of equilibration of portal venous and hepatic arteriolar pressures minus a small pressure gradient which occurs across the sinusoids There is an average increase in wedged hepatic vein pressure of 20 or more millimeters of mercury above right atrial pressure in patients with portal hypertension The wedged hepatic vein pressure is only a few millimeters of mercury more than right atrial pressure in patients without liver disease and those with hepatic disease who do not have portal hypertension

albumin is increased more than 30 per cent over normal predetermined standards (Table 4, Fig. 16). A diffuse increase in uptake has been noted in patients with hepatic fibrosis; spotty localization has occurred in granulomas. No alterations have been seen with primary liver cell cancer or amoebic abscess of the liver (51).

The mechanism responsible for localization of radioactive iodine in selected areas is being investigated in several clinics. Decision as to whether a morphologic or biochemical alteration which increases uptake of albumin or iodine is responsible for the results obtained will increase the usefulness of this technic. It has been suggested that there is an increased concentration of the isotope because of special affinity of certain cells for the radioactive material or that the vascularity of the areas of pathology is responsible. Presumably the radioactive material enters a localized area through the perisinusoidal space and is found in higher concentration because of greater acceptance or decreased turnover.

Abdominal radioactive scans are made using 300 microcuries of radioactive iodinated human serum albumin as the tracer material Gamma radiation is measured with a Geiger scintillation counter 24 hours after the injection, over 42 coordinate rectolinear points at intervals of 5 cm from the nipple line to the intercostal line and from flank to flank

The chief value of radioactive survey technics is as a directional guide for needle biopsy of the liver Diagnosis of localized hepatic lesions such as metastatic malignancy, granulomas, liver abscess, hematoma, and focal necrosis or fibrosis has been difficult in the past Thoratrast studies which provided excellent localization are no longer employed because of the carcinogenic potential of this material In the experience of most workers, radioisotope studies have been of limited value because of the uncertainty of the nature of the localized lesion and the frequency of false-positives Blind punch biopsy has often been worthless because occult lesions are rarely engaged by the biopsy needle. A diagnosis of superficial localized anatomic abnormalities in the liver is facilitated by a combination of radioisotope localization and needle biopsy. Radioisotope survey technics increase ability to recover localized lesions where needle biopsy is contemplated as a blind procedure A

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FIG. 17 Photograph of catheter in left hepatic vein of patient with moderate nutritional cirrhosis Pressures are usually recorded from the right hepatic vein

Hepatic vein catheterization may be performed where facilities for cardiac catheterization are available (52a). Under fluoroscopic guidance a cardiac catheter is passed from the median antecubital vein of either arm into the right atrium. The pressure is recorded and the catheter is then introduced into the vena cava by turning its tip to point to the right and posteriorly. After entering a hepatic vein, usually in the right lobe, the catheter is advanced as far as possible into the liver substance until it is wedged in a small hepatic venule (Fig. 17). Pressures are measured and a continuous recording made as the catheter is withdrawn to the free hepatic veins. Difficulty may be encountered in patients with hepatic cirrhosis because of alterations of the caval orifice (54).

Estimation of wedged hepatic vein pressure may be of value in determining the need for surgical therapy for portal hypertension. Its chief source of error is the lack of certainty that there is proper wedging of the catheter tip (53c). This procedure is of particular help in evaluating the vascular bed in patients without hematemesis who may be considered for portal vein decompression because of rectal hemorrhage, ascites, or hypersplenism refractory to medical therapy (54). Occlusive venous catheterization of the liver is also a useful adjunct to liver biopsy and percutaneous splenography in separating intrahepatic and extrahepatic causes of portal hypertension (55). The wedged hepatic vein pressure is normal in noncirrhotic extrahepatic portal hypertension. It has not been of value in serial evaluation of patients following portal decompression, as wedged pressure remains high after surgery in advanced cirrhosis (56). Although portal hypertension is relieved, obstruction to flow may be sufficiently marked so that hepatic arterial inflow causes a persistence of a high intrasinusoidal pressure.

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4

ANATOMIC DIAGNOSIS

THE CLINICIAN may establish an anatomic diagnosis in patients with hepatic disease (Fig 18) by obtaining a needle or surgical biopsy of the liver Needle biopsies are more readily performed, and may be repeated serially (1). Surgical biopsies are sometimes difficult to interpret for they contain artefacts as a result of handling and exposure of the liver during laparotomy, and the use of anesthetic agents which temporarily alter morphology. Specific indications for 2000 needle biopsies and 60 surgical biopsies performed in the Jersey City Medical Center over an eight-year period included (a) hepatomegaly of undetermined etiology, (b) differential diagnosis of jaundice, (c) confirmation of a clinical diagnosis of primary hepatocellular disease or neoplasm of the liver, (d) serial therapeutic follow-up of patients with chronic liver disease, (e) splenomegaly of uncertain origin, (f) systemic disease of undetermined etiology; and (g) clinical research

NEEDLE BIOPSY OF THE LIVER

Preparation of Patient

Biopsies should be performed in a hospital where they may be carried out at the bedside The procedure should be painless. We have avoided analgesics whenever possible so that the patient can register all sensation of pain not controlled by local anesthesia

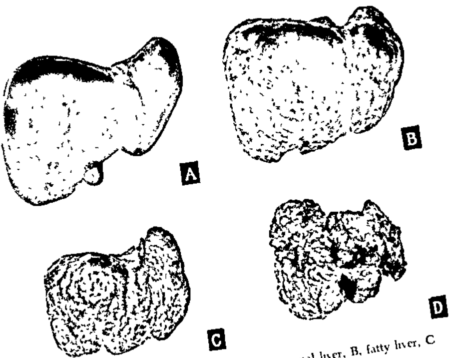


FIG 18 Gross appearance of the liver A, normal liver, B, fatty liver, C ... fibrosis of the liver, D, postnecrotic scarring

This permits the physician to detect postoperative abnormalities with greater facility. Apprehensive patients should be given a sedative, and those with hepatic tenderness should receive meperidine hydrochloride or morphine sulfate prior to the biopsy. Bleeding tendencies should be evaluated by a bleeding time, clotting time, capillary fragility, prothrombin time, and platelet count. Encountered abnormalities are corrected with vitamin K, vitamin C, and/or transfusion before biopsy.

Site of Biopsy

The size and position of the liver (as ascertained by palpation and percussion) determines the site of biopsy. Enlarged kidneys and abdominal tumors are differentiated from the liver by clinical and roentgenologic examination. The subcostal approach is desirable with a palpably enlarged liver, specimens being secured from either right or left lobes. The area between the xiphosternum and the right costal margin may be used in patients with a slightly enlarged liver. If the liver is of normal size or small, the needle should be inserted between the eighth or ninth rib in either the anterior or posterior axillary line, depending upon the habitus of the patient. In patients with suspected metastatic carcinoma or granulomas of the liver, use of radioisotope survey technics may provide area localization for needle biopsy (see Chapter Three).

Procedure

We have found the Vim Silverman needle (three and three-eighths inch) satisfactory for liver biopsies, and have used it exclusively in our studies (1c). The cutting edge of the needle must be kept sharp and an attempt made to avoid bends of the inner-split needle so as not to interfere with its entry into the outer encasement. *It is desirable to have the following equipment:*

1. Sterile gloves
2. Two per cent procaine solution
3. Two cubic centimeter syringe with hypodermic and #20 one-inch needle
4. Two (three and one-half inch) Vim Silverman needles

5 Sterile gauze
6. Sterile sheets

Needles which permit application of suction through a syringe are used with good results. Many clinics have modified such needles to embody a special principle (Iverson and Roholm (1a), Gillman (1k), Roth, Turkel (1l), etc) Peritoneoscopy has been combined with needle biopsy to permit gross inspection of the liver. This technic is largely reserved for patients with ascites Approximately 10 per cent of patients subjected to this procedure have diffuse abdominal pain and moderate ileus for several days

Needle biopsy is performed at the bedside with the patient lying on his back or left side Sterile precautions are employed including preparation of the skin with iodine and alcohol, and the use of sterile sheets and gloves. The skin, subcutaneous tissue, muscle and peritoneum are anesthetized with 2 per cent procaine solution A 3 mm skin incision is made with a Bard-Parker blade If there is continuous oozing of blood, bleeding tendencies are re-evaluated

The biopsy needle is introduced to *just inside* the capsule of the liver The stylet of the needle is removed and the split inner needle inserted to its full depth. The outer needle is advanced over the inner needle with rotary motion, holding the latter stationary Finally, the inner needle is turned and both needles are withdrawn simultaneously (Fig 19) The danger of excessive hemorrhage is decreased if the biopsy is kept close to the surface of the liver for major blood vessels are not likely to be in this area Resistance encountered to introduction of the biopsy needle provides a clue to diagnosis The normal liver is soft but offers intermediate resistance when compared with a fatty liver which exhibits little resistance or a severely fibrotic liver which is often stone hard

Patients are instructed to breathe quietly during the biopsy procedure for the intercostal approach This avoids marked motion of the needle in those unable to hold their breath in expiration and decreases the danger of liver laceration Slower and more meticulous manipulation of the needle is also possible with the intercostal technic, thereby increasing safety and the number

of successful biopsies The needle moves with respiration in this approach, and transfixation of the needle between the ribs does not occur Biopsies are done during full expiration or quiet breathing in the expiratory phase to avoid entering the lung parenchyma Firm pressure is applied over the biopsy site

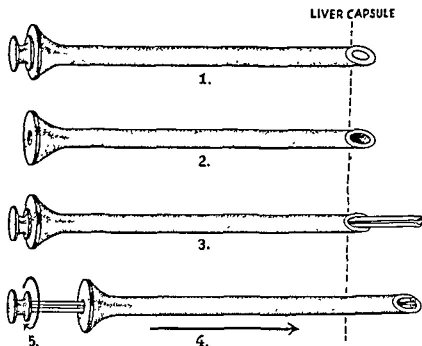


Fig 19 Technic of needle biopsy of the liver 1, Vim Silverman needle with stylet in place inserted to a point just inside liver capsule, 2, stylet removed, 3, inner bipronged needle inserted to full depth, 4, outer covering of Vim Silverman needle advanced over bipronged needle, 5, bipronged needle turned and both needles withdrawn simultaneously.

for 5–10 minutes to reduce bleeding from the liver wound The patient remains flat in bed for six hours following biopsy during which time pulse and blood pressure are recorded at two-hour intervals. Full ambulation is allowed after twenty-four hours.

Tissue Fixation and Staining

A liver biopsy specimen should be inspected for color, nodularity, and consistency. The normal liver biopsy is brownish-red;

it is green with obstructive jaundice, yellowish-brown with fat or fibrosis, and white with neoplasm or capsular fibrosis Ten per cent formalin is employed as a fixative The paraffin section is stained with hematoxylin and eosin or Gomori's trichrome stain Special stains are frequently desirable Absolute alcohol is used as a fixative and Best's carmine stain applied for glycogen studies. When fixed in formalin the frozen sections may be stained with scarlet red and hematoxylin to evaluate fat content Mallory's connective tissue stain and Gomori's trichrome stain are used for serial study of connective tissue Perl's reaction is employed for iron, crystal violet for amyloid, and Gomori's stain for alkaline phosphatase Lillie's nuclear stains are used for detailed cytologic studies (2)

Limitations of Needle Biopsy

Where there are localized anatomic abnormalities such as metastatic malignancy, the needle may not enter the involved area for only a small subcapsular portion of the liver is obtained on biopsy Radioisotope survey technics may aid in localizing lesions but deep anatomic abnormalities will always remain beyond the reach of the biopsy needle Waldstein and Szanto noted significant dissimilarity in lobular patterns, and the degree and location of fibrosis and inflammation in 10 per cent of their biopsy specimens (3). Interpretation of needle biopsy sections provided the same diagnosis as autopsy in 93 per cent of 100 patients receiving postmortem studies in the Jersey City Medical Center. Biopsy sections did not reveal metastatic carcinoma which was present in seven patients

Needle biopsies occasionally contain portions of the liver capsule which simulate fibrosis Specimens which do not contain the portal or centrilobular area are inadequate Localized lesions in these parts of the lobule are not detected, and it is difficult for the pathologist to orient himself.

Contraindications

Contraindications to liver biopsy include abnormalities in blood coagulation, suspected liver abscess, sepsis, acute congestive heart failure, lack of cooperativeness, absence of liver dullness,

and severe debility *Needle biopsy of the liver should not be undertaken with a significant abnormality of prothrombin time, prothrombin consumption time, bleeding time, clotting time, platelet count, or capillary fragility* Sepsis and anemia should be controlled prior to the procedure. It is desirable to defer biopsy in patients with acute passive congestion of the liver.

Needle biopsy is performed with great difficulty in uncooperative patients. Infants and children must be manually restrained until the biopsy is completed Nervous adults require soporifics and analgesics. Explanation of the procedure sometimes helps to allay anxiety, but occasionally increases apprehension.

Lack of liver dullness due to free peritoneal air or interposition of gut between the liver and abdominal wall constitutes a relative contraindication to liver biopsy. Patients with severe debility due to cachexia, anemia, peripheral vascular collapse, etc., should not be subjected to the procedure until their clinical state has improved

Complications

Complications of needle biopsy of the liver vary *Damage to neighboring organs, tumor cell implantation in the needle tract, bile peritonitis, infection, hemorrhage, shock, pain, and death may occur* (4) A review of the literature suggests the over-all risk of needle biopsy of the liver when properly carried out comprises a mortality of 0 1 per cent and a morbidity of 0 3–0.4 per cent (5).

Biopsy of other organs or tumors is avoided by careful appraisal of the patient. Unless one is certain an abdominal mass is the liver, it should not be biopsied However, it is easy to biopsy one of the kidneys if the needle is introduced too far posteriorly Metastatic carcinoma of the omentum, which simulated enlargement of the left lobe of the liver, was biopsied on two occasions Another time, a large distended gallbladder was entered in a patient who had biliary obstruction and metastatic carcinoma of the liver secondary to a pancreatic neoplasm.

Death from bile peritonitis following needle biopsy in a jaun-

diced patient has been recorded by several clinics (5) Few patients in our experience have developed peritoneal irritation despite the presence of intense icterus When slight peritoneal reactions are present, large bile capillaries have been evident on histologic section. Bile peritonitis probably represents an accident not related to technic or selection of patients. A small bile leak always occurs with a biopsy in which the portal triads are included in the specimen In one of our patients a relatively large bile capillary was discovered close to the surface of the liver and 2 cc. of pure bile was obtained by aspiration with the one-inch #20 gauge needle used for anesthesia

A small pneumothorax is sometimes induced in patients receiving an intercostal biopsy. This can be avoided by introducing the needle through the lowermost portion of the costophrenic sulcus Emphysema or displacement of the liver may necessitate introduction of the needle through lung tissue A localized purulent peritonitis followed needle biopsy in a patient with unsuspected pyogenic liver abscess. In contrast, none of three patients with amoebic liver abscess developed complications from needle biopsy performed because of diagnostic difficulty

Hemorrhage constitutes the most serious complication of needle biopsy of the liver (4) Fifteen to 30 ml of blood are lost at operation when the normal liver is biopsied with a Vim Silverman needle This is decreased with a fatty or fibrotic liver and increased with passive congestion of the liver Blood loss is due to interruption of the continuity of small branches of the portal vein, central vein, hepatic artery, and sinusoids of the hepatic lobules. The needle is sometimes introduced into an interlobular or interlobar vessel

No ill effect results from extravasation of small amounts of blood beneath Glisson's capsule during needle biopsy of the liver Bleeding from the puncture wound ceases as a result of the normal clotting process Defective coagulation can cause a fatal hemorrhage One patient with a hemorrhagic tendency died following a liver biopsy in our clinic This occurred early in our experience Using the precautions and contraindications listed

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Complications of needle biopsy of the liver vary. *Damage to neighboring organs, tumor cell implantation in the needle tract, bile peritonitis, infection, hemorrhage, shock, pain, and death may occur* (4). A review of the literature suggests the over-all risk of needle biopsy of the liver when properly carried out comprises a mortality of 0.1 per cent and a morbidity of 0.3–0.4 per cent (5).

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Death from bile peritonitis following needle biopsy in a jaun-

dice. In their correlative evaluation, the clinical diagnosis was incorrect and biopsy positive in 39 (19.3 per cent) of 202 patients with cirrhosis, in 28 (18 per cent) of 156 patients with hepatitis, in 13 (15.9 per cent) of 82 patients with neoplasm of the liver, in 12 (21.8 per cent) of 55 cases of obstructive jaundice, in 55 (64 per cent) of 86 cases of fatty vacuolization of the liver, and in 15 (34.9 per cent) of 43 cases of granulomatous disease of the liver.

Serial evaluation of patients with established liver disease has constituted the chief indication for needle biopsies performed in our clinic. Results of these studies emphasize the importance of periodic clinical, biochemical, and histologic evaluation. Although on random studies there is frequently no relationship between morphology and other findings (1j), comparative sequential observations provide good correlation. Signs and symptoms, and biochemical changes are related to activity in the connective tissue stroma, and the degree of interruption of normal vascular, biliary, and lymphatic relationships. These reflect the functional status of parenchymal cells. Clinical abnormalities are also correlated with necrosis, fat, inflammation, nodular regeneration of liver cells, and bile duct proliferation. These morphologic alterations provide an additional objective in treatment and further define limitations of current therapeutic approaches (6).

INTERPRETATION OF NEEDLE BIOPSY

Histologic sections should be jointly interpreted by the pathologist and clinician after reviewing etiologic, biochemical, and clinical data. Morphologic alterations can then be used for therapeutic orientation. The central and portal areas should be located and abnormalities described in relation to them (Fig. 20). Identification of the acinar area described by Rappaport (7) as the functional and anatomic center of the lobule is also helpful in abnormal biopsy specimens. The relative amounts of fibrosis, fat, regenerative phenomena, bile stasis, inflammation, necrosis

above, we encountered no major bleeding in either the Jersey City group or in a large series at St Albans Naval Hospital.

Pain occurs during the procedure if the needle is introduced through unanesthetized tissue As a result transient peripheral vascular collapse may occur Pain which develops following biopsy is usually due to extravasation of large amounts of blood, introduction of air into the subcapsular or pericapsular area of the liver, or bleeding into the pleura or peritoneum. Severe pain and ileus persisted for forty-eight hours in three patients with subcapsular hemorrhage following a biopsy. Two patients had severe chest pain following intercostal biopsies where radiographic studies demonstrated pericapsular air. A mild pleuritis or peritoneal irritation accompanied by a friction rub has been found in several patients who complained of mild pain after liver biopsy.

Justification for Needle Biopsy

Liver biopsy is desirable in patients with suspected hepatic disease, except for a well delineated acute process such as viral hepatitis, biliary obstruction, or acute passive congestion. Clinicians agree it is desirable where diagnostic problems are present. Its value in differential diagnosis of jaundice and hepatomegaly of uncertain origin is well documented A definite diagnosis of liver involvement in malignancy, amyloidosis, granulomatous disease, or hemosiderosis is possible only by this technic. Liver biopsy is equally important in establishing the histologic phase of subacute and chronic hepatic disease

The diagnostic value of needle biopsy has been reviewed in a series of 1000 patients studied by Schiff and associates at the Cincinnati General Hospital (5). Biopsies confirmed the clinical diagnosis in one half of the patients (49 2 per cent), corrected it in one fourth (24 7 per cent), were noncontributing to diagnosis in 16 6 per cent, misleading in 3 5 per cent, and inadequate in 6 per cent. Microscopic examination of needle specimens corrected wrong clinical impressions in 89 patients with suspected cirrhosis, 22 with suspected metastatic neoplasm, 30 patients felt to have viral hepatitis, and 10 felt to have obstructiv

nective tissue is found throughout the lobule, postnecrotic scarring in which connective tissue is seen in large bands adjacent to normal or regenerated parenchyma, and localized fibrosis in which connective tissue is limited to the centrilobular or portal area. Diffuse fibrosis occurs in nutritional cirrhosis, postnecrotic scarring is seen as a complication of viral and toxic hepatitis, centrilobular fibrosis occurs in heart failure, and portal fibrosis is seen in biliary obstruction.

Serial needle biopsy of the liver suggests hepatic fibrosis is due principally to proliferation of connective tissue in the site of liver cell injury, while condensation of reticular fibers is contributory (8). Hepatic fibrosis may result from nutritional deficiency, biliary obstruction, toxic and infective agents, passive congestion, or a combination of these factors. Fibroblastic proliferation in an area of inflammation occurs with and without liver cell necrosis, and is responsible for converting a localized process into a diffuse one. The degree of fibroblastic transformation varies directly with the inflammatory reaction and inversely with liver cell necrosis. It has been suggested that fibrosis usually represents a secondary phenomenon in hepatic cirrhosis and results from condensation of reticular tissue of lobules which have been destroyed and pushed aside by regenerating liver cells. The primacy of fibrosis in many instances is indicated by the frequent demonstration of progressive connective tissue changes in the absence of nodular regeneration of liver cells, and by the recognized ability to alter activity and quantity of connective tissue without significantly affecting parenchymal cells.

Fibroblasts, ground substance, and collagen fibers can be identified in the connective tissue stroma of hepatic cirrhosis. Fibroblastic activity may be assayed by quantitative analysis and morphologic characteristics of fibroblasts. It is normal to find a few spindle-shaped fibroblasts with vesicular or densely stained nuclei. Fibroblastic proliferation is characterized by a marked increase in these cells. Fibroblasts, which are directly or indirectly responsible for deposition of ground substance and development of reticular fibers, readily grow in tissue cultures of normal and cirrhotic liver biopsies (Fig. 21).



FIG 20 Section of a normal liver biopsy showing radiating cords of liver cells and a central vein

and other alterations should be determined and a pathologic diagnosis established.

Fibrosis

Special stains are necessary to estimate the quantity of connective tissue in liver biopsy specimens. Collagen fibers and fibroblasts are seen on routine study. However, special technics are required to evaluate "ground substance." There are three common types of hepatic fibrosis, diffuse fibrosis in which con-

which is the precursor of collagen (10) Fibrin does not appear to be essential for this process, although its presence in areas of inflammation accelerates the production of connective tissue. The ground substance is a mucopolysaccharide protein complex which is secreted by fibroblasts and mast cells. It is hydrophilic and may store water and electrolytes. Fibrils spun off the surface of fibroblasts coalesce to form collagen which is a relatively insoluble protein (9b).

Pathogenetic mechanisms leading to hepatic fibrosis will be described in Chapter 7 and 10 Regardless of etiology, fibrosis is classified on the basis of its amount and character, and dissociation of parenchymal cells from the vascular and biliary systems In mild fibrosis, the connective tissue is young, appears in thin bands and occupies less than 10 per cent of the histologic section. Moderate fibrosis is characterized by well developed connective tissue which contains newly formed blood vessels and bile ducts The fibrotic process occupies over 10 per cent of the section. In severe fibrosis, connective tissue virtually isolates parenchymal cells and causes complete distortion of the lobular pattern

Postmorten analysis of the cirrhotic liver shows an actual increase in collagen connective tissue (11) The important role of connective tissue proliferation in hepatic fibrosis is also revealed by reconstruction of serial sections and statistico-geometric analysis of necropsy material (12) Condensation of reticulum is often important in early phases of fibrogenesis, active growth of collagen fibers occurs secondarily Connective tissue septum formation is responsible for subdivision of the lobule

Increased connective tissue activity and a transition from mild to moderate to severe hepatic fibrosis is noted when therapy is not available or successful Although the fibrotic reaction serves as a reparative mechanism, necrosis and inflammation often continue or increase with connective tissue proliferation Therapy for patients with mild fibrosis causes improvement in clinical, biochemical and histologic abnormalities Regeneration of parenchymal cells improves hepatic architecture when proliferation of connective tissue causes hepatic fibrosis and returns it to normal when condensation of reticular fibers is primarily responsible

Inflammatory reactions are accompanied by an increased number of fibroblasts Following trauma or inflammation, leukotaxine is elaborated in the damaged tissue. This substance is responsible for an increase in capillary permeability and an influx of polymorphonuclear leukocytes, lymphocytes, and monocytes into the damaged area New fibroblasts appear if trauma



FIG 21 Fibroblasts grown in tissue culture of a biopsy from nutritional cirrhosis The source of the specimen and technic employed determine whether parenchymal cells or fibroblasts grow (Phase contrast microscopy)

is such as to lead to sclerosis or fibroplasia. These fibroblasts evolve chiefly from undifferentiated mesenchymal cells lying near the blood vessels, but may be derived from macrophages or even lymphocytes (9)

Electronmicroscopy indicates fibroblasts develop from mesenchymal cells, deposit ground substance, then spin off reticulum

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(8). Neither connective tissue proliferation nor condensation of reticular fibers due to liver injury is spontaneously progressive (13) Both may be controlled by therapy.

Inflammation

Mononuclear cells, lymphocytes, eosinophiles, or polymorphonuclear leukocytes may be seen in the connective tissue stroma of the liver There is a type and distribution of inflammation which is characteristic of certain hepatic lesions. Viral hepatitis is associated with an infiltrate whose character changes as the disease progresses Initially, there are numerous mononuclear cells with a moderate number of lymphocytes and an occasional eosinophile in the intralobular and interlobular areas. A gradual decrease in these cells occurs with healing. Extrahepatic obstructive jaundice is accompanied by periportal collections of lymphocytes and polymorphonuclear leukocytes. Fatty liver and nutritional cirrhosis are associated with focal collections of lymphocytes. Kupffer cell proliferation accompanies inflammation in tuberculosis, brucellosis, Boeck's sarcoid, histoplasmosis, and typhoid fever.

Control of etiologic factors may be accompanied by subsidence of an inflammatory reaction Inflammation has been classified as one plus with localized collections of mononuclear cells, lymphocytes, or polymorphonuclear leukocytes; two plus with intralobular and periportal collections of mononuclear cells, lymphocytes or polymorphonuclear leukocytes; three plus with numerous inflammatory cells throughout the lobule of the liver, and four plus with granuloma or abscess formation.

Fat

Fatty metamorphosis is seen in biopsies of patients with liver disease associated with an absolute or relative deficiency of lipotropic substances Fat accumulates in the form of intracellular and/or extracellular droplets Intracellular fat is difficult to differentiate from glycogen and other substances, and may require special stains for confirmation. Histochemical studies may demon-

strate both fat and glycogen droplets contribute to liver cell vacuolation in an individual patient. Extracellular fat is recognized more readily for it is not simulated by other substances. Varying stages in the development of extracellular fat are evident in biopsy specimens (14) (see Chapter 7) Intracellular fat merges to form large fatty globules which displace the liver cell nucleus. Rupture of membranes surrounding fat globules leads to formation of extracellular fatty cysts Fat accumulates first in the central zone and later in areas of the lobule farthest removed from the portal blood Fat may be present as the only histologic abnormality or occur in association with inflammatory hepatitis, bile stasis, or fibrosis. It is often present in the pseudolobules of nutritional cirrhosis

Fatty changes have been graded one plus when fat globules occupy less than 10 per cent of the section (Fig 22), 2 plus when they occupy between 10 and 30 per cent of the section (Fig. 22B), 3 plus when they occupy 30–80 per cent of the section (Fig 22C), and 4 plus when more than 80 per cent is occupied (Fig 22D)

Regeneration

Regenerative phenomena include mitoses, multiple nuclei, and nodular hyperplasia of liver cells, bile duct proliferation, and angiogenesis Liver cell mitoses are most prominent at the border of necrotic, inflammatory, or fatty areas Regeneration of liver cells is responsible for formation of pseudolobules which consist of nodules two or more cell layers thick These pseudolobules displace the central vein and contribute to portal hypertension by exerting pressure on surrounding sinusoids They are frequently the site of fatty changes and necrosis, and may be the precursors of adenoma or primary liver cell cancer Baggenstoss feels that nodular regeneration of liver cells is the most important abnormality in hepatic cirrhosis and is responsible for distortion of the normal lobular architecture and vascular patterns In this view fibrous connective tissue represents the accumulated skeletons of previously destroyed lobules or parts of lobules which have

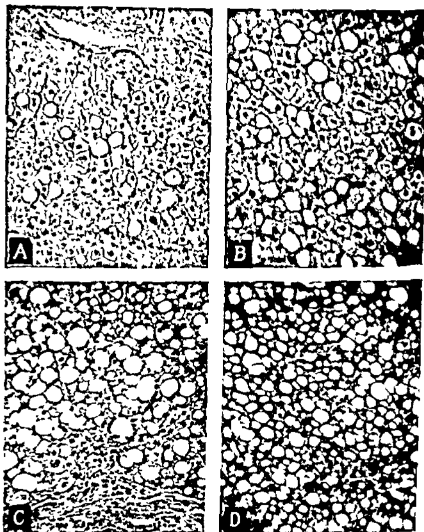


FIG 22. Histologic classification of fatty liver A, fat occupying less than 10 per cent of biopsy section, B, mild fatty liver, C, moderate fatty liver, D, severe fatty liver (Leevy, Zinke, White and Gnassi, A.M.A Arch Int Med., 92 527, 1953).

been pushed aside by the regeneration of hepatic cells (15) Our observations support the importance of nodular regeneration of liver cells but indicate an equally significant role for connective tissue proliferation in both initiating and perpetuating physiochemical abnormalities in cirrhosis

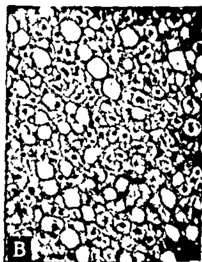
Bile duct proliferation is conspicuous in patients with biliary obstruction or infection, but it also occurs in other types of chronic liver injury Newly formed bile ducts are usually identical to normal ducts but sometime are made of cuboidal epithelium and do not contain a lumen Uncontrolled regeneration theoretically leads to bile duct cancer. Angiogenesis is most prominent in the connective tissue stroma and is eventually responsible for a bivenous capillary network which connects portal and hepatic veins (16).

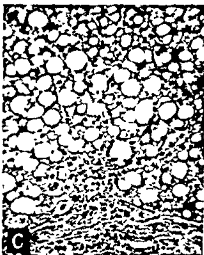
Regeneration has been classified as 1–2 plus with mitoses, double nuclei, and bile duct proliferation, and 3–4 plus with the finding of pseudolobules

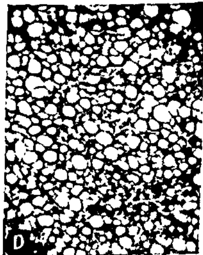
Bile Stasis

Bile may be detected in capillaries, canaliculi or ducts of the biliary system Bile stasis due to extrahepatic biliary obstruction must be differentiated from that occurring in intrahepatic processes. In the early phases of extrahepatic biliary obstruction, bile plugs occur in the center of the lobules, inspissated bile is found in intralobular bile ducts, and pigmentation is noted in both liver cells and Kupffer cells (16b) Continued biliary obstruction leads to portal inflammation and fibrosis In contrast, intrahepatic processes are usually accompanied by necrosis or fatty metamorphosis and inflammation An exception occurs in patients with arsenical intoxication, hematogenous bacterial infection, or viral infection where a functional abnormality of the cholangioles is responsible for cholestasis and liver cell morphology is normal Bile stasis has been classified as 1–2 plus when bile pigment is present in intracellular capillaries and intralobular canaliculi, and 3–4 plus when bile is found in larger bile ducts and in lakes in the parenchyma









... ver A, fat occupying less than
... liver, C, moderate fatty liver,
... and Gnassi, A M A. Arch Int

to one or more areas of the hepatic lobule, and 3–4 plus with autolytic necrosis

Miscellaneous Pathologic Findings

Hemosiderosis of the liver may occur as a complication of primary hepatic disease, develop as a result of an inborn or acquired error of iron absorption, or follow intravenous iron or transfusion therapy Iron may be localized in the parenchymal cell, Kupffer cells, or both. Characteristically, iron is initially deposited in the parenchymal cells with increased intestinal absorption It is first taken up by the Kupffer cells with parenteral iron or blood transfusions Both areas become involved with increasing amounts of iron deposition Hemosiderin is identified by the Prussian blue reaction and biopsies which exhibit pigment of undetermined type should be routinely subjected to this test

Extramedullary hemopoiesis is found in liver sections in a large number of patients with chronic systemic diseases Erythroblasts and megakaryocytes are seen in the sinusoids An etiologic mechanism for myeloid metaplasia may be determined by needle biopsy where there is previously unsuspected granulomatous or neoplastic disease

Amyloid is deposited in the liver between the endothelial cells of the sinusoids and the hepatic cords, and in blood vessels of the portal area Small amounts of amyloid may be overlooked in needle biopsies unless special stains are employed In primary amyloid where there is no specific etiologic factor, staining may be achieved in most instances with methyl violet or crystal violet Congo red or iodine is used to stain amyloid which is secondary to chronic inflammatory and degenerative diseases Staining qualities of the amyloid accompanying multiple myeloma varies

COMMON PATHOLOGIC DIAGNOSES

Normal Liver

A diagnosis of "normal liver" is made in the presence of normal structure and cytology An intact lobule which includes a central

Liver Cell Degeneration and Necrosis

Hydropic swelling, cytoplasmic alterations and nuclear changes may precede liver cell death. Hydropic degeneration is seen in a variety of chronic illnesses. It has been attributed to anoxia and in animal experiments it has occurred with exposure to low atmospheric pressure and chemical intoxication. Cytoplasmic and nuclear changes accompany necrosis.

The type and location of necrosis in large part determines the prognosis in liver disease (17). Necrosis is recognized by changes in the cell body and in the nucleus. Normal cell boundaries may become indistinct and cytoplasm loses its normal reticulated appearance. Nuclear changes include dissolution of chromatin (chromatolysis or karyolysis), fragmentation of the nucleus (karyorrhexis), and condensation of nuclear material (pyknosis). Needle biopsy sections may show simple, basophilic coagulative, hyaline, autolytic, or caseation necrosis. Simple necrosis is characterized by swelling and vacuolation of liver cells with or without nuclear changes and is seen in all varieties of hepatic disease. Eosinophilic coagulative necrosis is seen in viral hepatitis, infectious mononucleosis and other viral diseases. Acidophilic cytoplasm becomes compact and forms a hyaline body. Hyaline necrosis is most often present in nutritional cirrhosis and is common after bouts of acute alcoholism. A red, homogenous body which stains deeply with eosin is present in the liver cell. Autolytic necrosis with complete disappearance of parenchymal cells in the area of involvement occurs in fulminant viral hepatitis, some instances of heavy metal intoxication, and occasionally in circulatory congestion due to shock or heart failure. Caseation necrosis is characteristic of tuberculosis and syphilis.

Necrosis may be localized to one area of a lobule (zonal), occur in patchy areas (focal), or involve the entire lobule (massive). Zonal necrosis usually occurs in the area surrounding the central vein (centrilobular), but may appear in the acinar area (midzonal), or near the portal triad (periportal).

Necrosis has been classified as 1–2 plus when it is localized





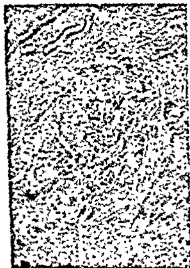




FIG. 23 Histologic classification of hepatic cirrhosis (connective tissue represented in blue, trichrome stain). *Top left* Mild cirrhosis with fat. *Top right* Moderate cirrhosis. *Bottom left* Severe cirrhosis with inflammation in connective tissue stroma. *Bottom right* Hyaline necrosis (necrotic areas stained deep red).

vein and portal triad must be present for this designation to be employed

No Significant Abnormalities

The label "no significant abnormalities" is used in biopsies in which it is not possible to demonstrate an intact lobule. Biopsy specimens which are completely normal except for minimal increase in connective tissue, less than 10 per cent fat, occasional proliferation of bile ducts, slight inflammation, or simple necrosis are also placed in this category

Fatty Liver

A diagnosis of "fatty liver" without fibrosis is made in patients whose biopsy section is occupied by more than 10 per cent fat (see Chapter 7). The fatty liver may contain varying amounts of inflammatory cells, necrosis, and bile stasis Fat is usually both extracellular and intracellular, but may occur in association with varying degrees of fibrosis. Occasionally fat is present with biliary obstruction, passive congestion, viral hepatitis, or neoplastic infiltration.

Nutritional Cirrhosis

A diagnosis of nutritional cirrhosis is based on an appropriate history plus diffuse fibrosis, bile duct proliferation, and regenerated lobules, with or without fatty and lymphocytic infiltration. The morphologic severity of the disease is determined by the degree of dissociation of the parenchymal liver cells from the vascular and biliary systems. From biopsy specimens we have classified nutritional cirrhosis into four categories: mild, moderate, and severe cirrhosis, and cirrhosis with hyaline necrosis. Fatty metamorphosis may be present in any of these categories. Mild cirrhosis is interpreted as representing the earliest stage of the disease Connective tissue is young and occurs in thin bands which often contain fibroblasts and occupies less than 10 per cent of the histologic section (Fig 23 top left) Moderate cirrhosis is characterized by well developed connective tissue which contains regenerated bile ducts and newly formed blood vessels

The fibrotic process is associated with nodular regeneration of liver cells (Fig 23 top right) In severe cirrhosis, the parenchymal cells are virtually isolated by well-developed fibrosis and there is complete distortion of the lobular pattern Connective tissue is interspersed with bile ducts and blood vessels (Fig 23 bottom left). Hyaline necrosis may be present in any of these stages of nutritional cirrhosis (Fig 23 bottom right).

Viral Hepatitis

Liver biopsy is the best method for making a definite diagnosis of acute nonfatal viral hepatitis (18) There is patchy necrosis and degeneration throughout the hepatic lobule which distorts liver cell continuity and regularity Liver cells are swollen and vacuolated, or shrunken and have an acidophilic cytoplasm They demonstrate mitotic and amitotic divisions There is a variability in the size and number of liver cell nuclei of intact cells. Degenerating cells exhibit pyknosis of the liver cell nucleus, and acidophilic cytoplasm separates from the cell membrane and is extruded in the form of hyaline bodies into the sinusoids (18b). Focal accumulation of monocytes, lymphocytes, histiocytes, polymorphonuclear leukocytes, and eosinophilic leukocytes is noted throughout the lobule and in the portal area Kupffer cells are increased in size and often contain lipochrome a golden brown, finely granular pigment

Three to four weeks after onset of jaundice, serial biopsies show less necrosis and inflammation Regeneration of liver cells is more marked and there is still evidence of ballooning and acidophilic degeneration Bile thrombi may be present in bile capillaries. Evidence of liver cell injury may persist for a period of four to six months but biopsies after three months are usually normal and exhibit no stigmas of a previous hepatitis With persistent or recurrent hepatitis varying degrees of necrosis inflammation Kupffer cell hyperactivity, and regeneration of liver cells are noted

Fulminant viral hepatitis is characterized by autolytic necrosis All of the cells in an entire lobule may disappear Inflammation is conspicuous at the periphery of the lobule and consists of mononuclear cells lymphocytes plasma cells and reticuloendothelial

cells in the affected area exhibit pyknosis, degeneration of nuclei, and eosinophilic staining of the cytoplasm. Biopsies from patients with long-standing or recurrent episodes of circulatory congestion show thickening of the central veins and centrilobular or diffuse fibrosis

Granulomas

Nonspecific granulomas are characteristic of many different diseases including tuberculosis, brucellosis, histoplasmosis, tularemia, syphilis, lymphogranuloma venereum, leprosy, actinomycosis, infectious mononucleosis, and beryllium intoxication Lesions are composed of mononuclear cells, multinucleate giant cells and a thin stroma of connective tissue There may be associated necrosis and in some instances hepatic fibrosis may occur in the granulomatous area Granulomas are frequently not associated with clinical or biochemical abnormalities, and the primary diagnosis must be established by history, physical findings, and laboratory studies including skin tests, complement fixation tests, etc. An etiologic diagnosis may be made in some instances by bacteriologic studies of biopsy material

Neoplasia

Primary liver cell cancer is characterized by a variable degree of organization into liver lobules, inversely proportional to the degree of malignancy Liver cells lose their granularity and tend to be basophilic with nuclei which show hyperchromatism and numerous mitoses (22) Blood vessel invasion is frequent.

In bile duct cancer, the liver lobule is invaded by cuboidal to tall columnar epithelial cells The tumor cells form round or oval aggregates and have many mitoses (23)

Metastatic carcinoma usually has characteristics of the primary lesion It is often possible to determine the location of a primary neoplasm from the histologic features of hepatic metastases Biopsy specimens frequently show areas of fibrosis or necrosis along with the neoplasm Often it is impossible to identify neoplastic cells in such biopsies. Comparative study of the histology of metastatic lesions to the liver and the primary site show varying degrees of cellular alteration of the metastatic lesion.

cells Regenerative hyperplasia of the surviving parenchyma is minimal and confined to the biliary epithelium (19). In some instances there is patchy autolysis of the liver lobules which is not accompanied by immediate death The necrotic reaction is accompanied by a pronounced inflammatory reaction and this is followed by regeneration of liver cells and bile ducts

Postnecrotic Cirrhosis

Postnecrotic cirrhosis is best identified by its gross appearance Large nodules of liver cells are conspicuous and are surrounded by broad areas of fibrous connective tissue. Groups of normal appearing liver lobules occur adjacent to areas of regenerated cells. Hepatic cells in areas of injury are characterized by multiple hyperchromatic nuclei and contain acidophilic and vacuolated cytoplasm The connective tissue stroma contains numerous mononuclear cells, polymorphonuclear leukocytes, lymphocytes, and *fibroblasts Bile ducts and ductules are conspicuous, and inflammation* is seen in the walls of portal and hepatic vessels.

Biliary Obstruction

Biliary obstruction is characterized by bile stasis with varying degrees of inflammation and fibrosis (20). Bile may be present in the intralobular, interlobular, or main bile ducts. Bile pigment appears in both liver cells and Kupffer cells. Polymorphonuclear leukocytes, lymphocytes, and monocytes are present in the portal area and accompany newly formed bile ducts and connective tissue Continued biliary obstruction is followed by diffuse fibrosis which dissects the lobule and is accompanied by pronounced bile duct proliferation (biliary cirrhosis).

Passive Congestion

Passive congestion is characterized by dilatation and pooling of red blood cells in the central vein and sinuosids. Serous fluid may be demonstrable in the perisinusoidal space of Dissé and around the centrilobular veins (21). Congestion is greatest in the centrilobular area and is associated with local hemorrhage and necrosis of the liver cells In central necrosis there is intense congestion of the central vein and distention of the sinusoids. Dead or dying

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NEEDLE BIOPSY AND BIOCHEMICAL STUDIES

Attempts have been made to correlate chemical analysis of liver biopsies with morphology, clinical, and biochemical findings. All such studies are based on chemical analysis of a small amount of tissue which contains variable amounts of connective tissue septa, vascular tissue, bile ducts, and liver cells. A study in our clinic with Dr Leon Chesley demonstrated the futility of such analyses with present methods. An attempt was made to correlate the glycogen storage test with the glycogen content of liver biopsies. However, specimens obtained simultaneously from different areas of the liver showed as much as 100 per cent variation in chemically determined glycogen Postmortem studies of fatty liver show better consistency and demonstrate fair correlation of chemical and morphologic findings (21) However, there is no specific relationship between blood sugar and liver glycogen, liver lipids and blood lipids, or protein patterns and nuclear desoxypentose nucleic acids and cytoplasmic pentose nucleic acid (25). Further study is desirable in order to convert basic observations in histochemistry into practical applications on patients with liver disease. A method which permits chemical study of liver cells divested of their supporting structures would provide the first step towards this goal

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5

DIFFERENTIAL DIAGNOSIS

HEPATIC abnormalities are frequently suspected in the absence of liver disease because of confusing symptoms, signs or laboratory findings. (a) Patients with vague gastrointestinal symptoms, weakness, sensorial changes, hematemesis, melena, and bleeding tendencies are suspected of having liver disease (b) Upper abdominal masses, right upper quadrant tenderness or pain, jaundice, splenomegaly, ascites, and endocrine disturbances may be present in nonhepatic conditions and simulate liver disease. (c) Abnormalities in tests used to assay hepatic function sometimes allow an erroneous diagnosis of liver disease although extrahepatic mechanisms are responsible

SYMPTOMS AND SIGNS OF LIVER DISEASE

Weakness

Weakness and ease of fatigue are common complaints in patients who have recovered from acute liver disease The cause of these symptoms which are present also in chronic hepatic disease is not known Muscular weakness results from a number of biochemical abnormalities (1) Processes which interfere with the phosphate or thiol ester energy systems, or cause depletion of potassium, creatine glycogen, magnesium, or oxygen are characterized by myasthenia Decision that muscle weakness is not due to a sub-

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Hemorrhagic Tendency

Because of the importance of the role of the liver in normal hemostasis it is often necessary to evaluate hepatic function in patients with a hemorrhagic tendency. The relationship of abnormal bleeding to hepatic insufficiency is sometimes difficult to determine because of the coexistence of malnutrition, splenic hyperactivity, or constitutional defects Vitamin K and vitamin C deficiency may be responsible for hypoprothrombinemia and increased capillary fragility, respectively Splenic hyperactivity often causes thrombopenia or thrombasthenia Congenital defects such as hemophilia, hemophilioid states, parahemophilia, fibrinogenopenia, etc, may be latent until the onset of liver disease (5) A complete hematologic work-up with serial observations of responses to therapy is desirable in cases of obscure hemorrhagic tendency

Abdominal Masses

An enlarged right kidney, pancreatic cyst, hydrops of the gallbladder, neoplasm of the stomach or colon, or retroperitoneal mass is occasionally difficult to differentiate from a large liver (6) Physical examination frequently suggests a need for further study because of the absence of a typical hepatic contour X-ray study including tomography, pyelography, retroperitoneal air studies, cholecystography, and barium study of the gastrointestinal tract are helpful in differential diagnosis

Abdominal Tenderness

Acute cholecystitis and empyema of the gallbladder produce marked right upper quadrant tenderness which may be impossible to distinguish from a tender, enlarged liver This often causes a delay in surgical treatment of patients with acute gallbladder disease and leads to abdominal exploration in patients with primary liver disease Correlation of clinical data and laboratory findings decreases this error The presence of leukocytosis argues against primary liver disease unless there is a secondary infection, infarction of the liver, or cholemia

clinical or clinical disorder of the liver is difficult. In addition to routine hepatic studies, measures of glycogen storage capacity, estimation of total exchangeable potassium, and a therapeutic trial of a high carbohydrate, high vitamin intake may be helpful in evaluating and correcting this symptom

Mental Changes

Alteration of mental state due to hepatic insufficiency is difficult to differentiate from the sensorial changes found in deficiency states and toxic psychoses Any process which interferes with the supply of essential nutrients, enzymatic activity or oxygen utilization of cerebral cells results in impaired function. Studies of cerebral hemodynamics and metabolism demonstrate a similar decrease in cerebral oxygen consumption in hepatic coma, hypoglycemia, diabetic coma, uremic coma, pernicious anemia, cerebral arteriosclerosis, and the coma associated with brain tumors and trauma (2) Electroencephalographic tracings and findings on neurologic examination are not specific Diagnostic difficulty is increased because of the *frequency of thiamine deficiency, niacin* deficiency, anemia, uremia, or delirium tremens in patients with *liver disease These factors often potentiate each other to produce* mental changes

Gastrointestinal Hemorrhage

Gastrointestinal hemorrhage presents a complex diagnostic problem in many cases of suspected or proven liver disease. We have found peptic ulcer in 10 per cent of patients with nutritional cirrhosis. Other lesions such as gastric cancer, leiomyoma, and erosive gastritis also occur (3). Balloon tamponage has been of value as a therapeutic and diagnostic measure in the acute bleeding phase If bleeding continues after effective tamponage, causes other than esophageal varix hemorrhage should be considered. Barium studies of the upper gastrointestinal tract may be helpful in these instances (4). Emergency surgery is required if hemorrhage continues despite lack of a definite preoperative diagnosis If bleeding stops spontaneously, careful gastrointestinal x-rays, esophagoscopy, and/or gastroscopy will usually help to establish the diagnosis.

Table 5 Etiologic Factors in 438 Unselected Patients with Clinical Jaundice and Serum Bilirubin of more than 2.0 mg/100 cc

I Prehepatic Jaundice		
A Nonhemolytic		
1 Constitutional hyperbilirubinemia		2
2 Pulmonary infarction		22
3 Hematomas		3
4 Physiologic of newborn		57
B Hemolytic		
1 Intracorpuscular defects		11
a Congenital hemolytic jaundice	2	
b Sickle cell anemia	7	
c Mediterranean anemia	2	
2 Extracorpuscular		29
a Immune body reactions		
(1) Transfusions	10	
(2) Erythroblastosis	7	
b Infections and chemicals		
c Physical agents	3	
d Secondary hemolysis in malignancy	6	
II Hepatic Jaundice		
1 Hepatocellular		
a Hepatitis	71	
b Cirrhosis	90	
c Fatty liver	14	
d Liver abscess	4	
2 Hepatocanalicular		
a Viral or idiopathic	5	
b Arsenical	1	
III Posthepatic Jaundice		
1 Stricture	6	
2 Neoplastic	45	
3 Calculous disease	53	
IV Combination Causes of Jaundice		
1 Hepatic plus prehepatic	13	
2 Hepatic plus posthepatic	12	
3 Posthepatic plus prehepatic	4	

From Leevy and Emmert (7)

Jaundice

Decision as to the cause of jaundice is an important and difficult task which requires considerable diagnostic acumen. A correct diagnosis is facilitated by correlating evidence derived from clinical examination, biochemical studies, and liver biopsy. Problems in diagnosis arise because of confusing clinical features, the nonspecificity of biochemical liver function tests and other laboratory procedures, the difficulty in interpreting needle biopsy of the liver, and the presence of two or more causes for jaundice (7).

Jaundice may be divided into three types: prehepatic, hepatic, and posthepatic. Prehepatic jaundice results from production of bilirubin-protein beyond the disposal capacity of the reticuloendothelial system. This type may be due to hemolytic or nonhemolytic disease (Table 5). Hepatic jaundice is due to injury of liver cells which interferes with separation of bilirubin-protein or decreases the excretion of bilirubin. Posthepatic jaundice is due to obstruction of bilirubin outflow.

Signs and symptoms may be of considerable value. The symptom complex and physical signs classified by age groups permit a correct diagnosis as to the cause of jaundice in 75 per cent of the patients. For example, prehepatic jaundice is apparent when a patient has onset of icterus with chills and fever during a whole-blood transfusion. Hepatic jaundice is suspected in the icteric alcoholic patient with poor dietary habits. Posthepatic jaundice should be the first consideration when a patient with previous biliary colic develops icterus and right upper quadrant pain.

Age is helpful. All except 5 out of 76 newborn infants with jaundice observed at the Margaret Hague Maternity Hospital in Jersey City over a period of five years had prehepatic icterus. Hepatic jaundice due to viral hepatitis "I.H." occurs predominantly between the ages of 12 and 30, and that due to nutritional cirrhosis between 40 and 60. Most patients with posthepatic jaundice are over 50 years of age. Viral hepatitis "S.H." following injections or transfusions occurs in each of the groups and decreases the significance of age in diagnosing the cause of jaundice.

Table 5 Etiologic Factors in 438 Unselected Patients with Clinical Jaundice and Serum Bilirubin of more than 2 0 mg /100 cc

I. Prehepatic Jaundice		
A Nonhemolytic		
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2 Pulmonary infarction		22
3 Hematomas		3
4 Physiologic of newborn		57
B Hemolytic		
1 Intracorpuscular defects		11
a Congenital hemolytic jaundice	2	
b Sickle cell anemia	7	
c Mediterranean anemia	2	
2 Extracorpuscular		29
a Immune body reactions		
(1) Transfusions	10	
(2) Erythroblastosis	7	
b Infections and chemicals		
c Physical agents	3	
d Secondary hemolysis in malignancy	6	
II Hepatic Jaundice		
1 Hepatocellular		
a Hepatitis	71	
b Cirrhosis	90	
c Fatty liver	14	
d Liver abscess	4	
2 Hepatocanalicular		
a Viral or idiopathic	5	
b Arsenical	1	
III Posthepatic Jaundice		
1 Stricture	6	
2 Neoplastic	45	
3 Calculous disease	53	
IV Combination Causes of Jaundice		
1 Hepatic plus prehepatic	13	
2 Hepatic plus posthepatic	12	
3 Posthepatic plus prehepatic	4	

From Leevy and Emmert (7)

Jaundice

Decision as to the cause of jaundice is an important and difficult task which requires considerable diagnostic acumen. A correct diagnosis is facilitated by correlating evidence derived from clinical examination, biochemical studies, and liver biopsy. Problems in diagnosis arise because of confusing clinical features, the nonspecificity of biochemical liver function tests and other laboratory procedures; the difficulty in interpreting needle biopsy of the liver, and the presence of two or more causes for jaundice (7).

Jaundice may be divided into three types prehepatic, hepatic, and posthepatic Prehepatic jaundice results from production of bilirubin-protein beyond the disposal capacity of the reticuloendothelial system This type may be due to hemolytic or nonhemolytic disease (Table 5). Hepatic jaundice is due to injury of liver cells which interferes with separation of bilirubin-protein or decreases the excretion of bilirubin. Posthepatic jaundice is due to obstruction of bilirubin outflow.

Signs and symptoms may be of considerable value. The symptom complex and physical signs classified by age groups permit a correct diagnosis as to the cause of jaundice in 75 per cent of the patients For example, prehepatic jaundice is apparent when a patient has onset of icterus with chills and fever during a whole-blood transfusion Hepatic jaundice is suspected in the icteric alcoholic patient with poor dietary habits. Posthepatic jaundice should be the first consideration when a patient with previous biliary colic develops icterus and right upper quadrant pain.

Age is helpful All except 5 out of 76 newborn infants with jaundice observed at the Margaret Hague Maternity Hospital in Jersey City over a period of five years had prehepatic icterus. Hepatic jaundice due to *viral hepatitis "I H" occurs predominantly* between the ages of 12 and 30, and that due to nutritional cirrhosis between 40 and 60 Most patients with posthepatic jaundice are over 50 years of age Viral hepatitis "S H" following injections or transfusions occurs in each of the groups and decreases the significance of age in diagnosing the cause of jaundice.

Table 6 Biochemical Findings in Uncomplicated Jaundice*[a]

	Prehepatic	Hepatic	Posthepatic
Reticulocyte count	Over 5%	1–3%	1–3%
Prompt reacting bilirubin	0.3–0.5 mg%	0.5 mg%	0.5 mg%
Delayed bilirubin	0.5 mg	0.5 mg	0.3–0.5 mg
Bile in urine	0	0–4+	1–4+
2-hour urobilinogen in urine	1.5 Eh U	Variable	0–0.65 Eh U
Alkaline phosphatase	0–5 B U	0–15 B U	5–30 B U
Total cholesterol	180–250 mg %	Variable	250 mg %
Cholesterol esters % of total	60–70%	50%	60–70%
Serum albumin	3.5–5.0 Gm %	3.5–5.0 Gm %	3.5–5.0 Gm %
Serum globulin	1.5–2.5 Gm %	1.5–2.5 Gm %	1.5–2.5 Gm %
Cephalin flocculation	0–1	2+–4+	0–1+
Thymol turbidity	0–4.0 U	4.0 U	0–4.0 U
Galactose tolerance	5 mg % retained in 75 min	5 mg % retained in 75 min	5 mg % retained in 75 min
Glycogen storage blood sugar rise	40–60 mg % rise	40 mg % rise	40–60 mg % rise
Prothrombin time response to vitamin K	Return to normal	No response	Return to normal

* Modification of these values is necessary in the newborn infant

[a] Reproduced from Leevy and Emmert, *Rev Gastroenterology* 20 422, 1953

Knowledge of exposure to hepatotoxic agents furnishes a clue to diagnosis A history of biliary colic is helpful since it occurs in 40 per cent of patients with posthepatic jaundice and in less than 2 per cent of patients with other types of jaundice. Symptoms of anemia, gastrointestinal disturbances, and fluid retention are less specific.

Physical findings are sometimes of diagnostic aid. The presence of a palpable gallbladder is a sign of posthepatic jaundice. Spider angiomas and evidence of collateral circulation are usually characteristic of hepatic jaundice. These signs are also seen in the late phases of posthepatic jaundice with marked secondary liver injury A combination of liver tenderness, hepatomegaly, and splenomegaly suggests hepatic disease, but the findings are present also in other causes of jaundice Thus, hepatic tenderness is a conspicuous feature in biliary obstruction and the spleen is often large in hemolytic disease.

Biochemical study permits a correct diagnosis (7) of the general cause of jaundice in 80–85 per cent of patients (Table 6). Errors result principally from reliance on one or two tests. Studies of bilirubin metabolism offer the simplest means of differentiating jaundice. Fractionation of serum bilirubin is helpful in supporting the diagnosis of hemolytic jaundice, but is of limited value in differentiating biliary obstruction and hepatocellular disease (8). Urine and fecal bile and urobilinogen are useful tests in uncomplicated prehepatic and posthepatic jaundice An elevation of the serum alkaline phosphatase is valuable in recognition of posthepatic jaundice although cholangiolitic hepatitis and metastatic malignancy are also accompanied by increased levels of this enzyme. A normal serum alkaline phosphatase favors prehepatic or hepatic jaundice Low cholesterol esters, positive flocculation tests, poor prothrombin response to vitamin K, and decreased tolerance to galactose are indicative of primary liver disease or suggest secondary hepatic injury is present in patients with hemolytic disease or biliary obstruction

Needle biopsy of the liver is the most effective means of differentiating hepatic jaundice from posthepatic and prehepatic jaundice. It is the only method of diagnosing the specific cause of

	October 1948	March 1949	March 1950	March 1951
Biochemical study				
Serum bilirubin (mg %)	0 3	0 7	2 1	31 0
Bromsulfalein (%)	30	16	25	80
Serum alkaline phosphatase (B U)	3 4	4 2	4 5	19 2
Total serum cholesterol (mg %)	250	393	380	465
Cholesterol esters (mg %)	110	253	240	110
Serum albumin (Gm %)	3 4	3 6	3 5	3 5
Serum globulin (Gm %)	3 8	4 1	4 1	4 0
Cephalin flocculation	4+	4+	4+	4+
Thymol turbidity (units)	5 0	4 0	4 0	4 0
Galactose tolerance (mg %)	15	10		15
Histologic study				
Fibrosis	3+		3+	3+
Fat	1+		1+	0
Regeneration	3+		3+	3+
Bile stasis	0		0	3+
Infiltration	2+		2+	2+
Necrosis	0		0	0
Other	0		0	0
Pathologic diagnosis	Nutritional cirrhosis moderate		Nutritional cirrhosis moderate	Nutritional cirrhosis with bile stasis

Comment This case history illustrates the difficulty in making an early diagnosis of extrahepatic biliary obstruction in patients with established liver disease Clinical and biochemical studies were not diagnostic initially and the elevated serum bilirubin was erroneously attributed to progression of hepatocellular disease Serial follow-up led to a clear pattern of biliary obstruction, but at this time the neoplasm was inoperable

CASE 4 SICKLE CELL DISEASE WITH RECURRENT HEMOLYTIC CRISES, AND INTERCURRENT VIRAL HEPATITIS (S H)

Clinical Features F.P , a 22-year-old laborer, was repeatedly hospitalized because of hemolytic crises and chronic leg ulceration Crises were chacterized by low-grade icterus and polyarthritis Symptoms were controlled by bed rest, salicylates, multiple transfusions, and supportive therapy during 1947 and 1948 Marked icterus was noted in 1948

hepatic jaundice However, there is the possibility of bile peritonitis following needle biopsy in jaundiced patients. Abnormal bleeding tendencies which accompany hepatic jaundice constitute a further limiting factor A diagnosis of hepatic jaundice is made with characteristic histologic features of viral hepatitis, toxic hepatitis, central necrosis, nutritional cirrhosis, postnecrotic scarring, or centrilobular fibrosis. Liver biopsy may show erythrophagocytosis by Kupffer cells and puddling of red blood cells in sinusoids in prehepatic jaundice A diagnosis of posthepatic jaundice is made when the biopsy shows (a) bile stasis, bile casts, and intracellular bile granules, (b) biliary stasis with periportal or perilymphatic inflammation, or (c) biliary stasis with periportal fibrosis, bile duct proliferation and nodular regeneration of parenchymal cells (9)

Diagnostic problems are present despite clinical and laboratory studies in patients with two possible mechanisms contributing to their jaundice The following case histories are illustrative.

CASE 3 EXTRAHEPATIC BILIARY OBSTRUCTION SUPERIMPOSED ON NUTRITIONAL CIRRHOSIS

Clinical Features W S., a 54-year-old bartender, was hospitalized because of alcoholism He had eaten poorly and consumed 1–2 pints of whiskey daily for several years. A diagnosis of nutritional cirrhosis was made on the basis of clinical and laboratory studies. Eighteen months after initial study, the patient became jaundiced. Icterus was attributed to progression of his hepatic disease The true mechanism of progressive jaundice was not clear until 12 months later. Exploratory operation revealed an inoperable carcinoma of the head of the pancreas. Postmortem examination confirmed the clinical diagnosis

	October 1948	*March 1949*	*March 1950*	*March 1951*
Hepatomegaly	6 cm	6 cm.	7 cm	8 cm
Splenomegaly	2 cm	2 cm	2 cm	2 cm
Spider angiomas	+	+	+	+
Icterus	0	0	1+	4+
Fluid retention	0	0	1+	3+
Hepatic fetor	0	0	0	0
Sensorial changes	0	0	0	2+

cal and histologic studies are employed serially This case history illustrates the successful use of this technic Patients with nutritional cirrhosis who develop icterus after transfusions also may have a superimposed hepatitis The marked morphologic changes already present in cirrhosis interfere with recognition of stigmas of hepatitis

SPLENOMEGALY

Splenomegaly of nonhepatic origin is difficult to differentiate from an enlarged spleen secondary to liver disease Infiltrative neoplasms including cysts and hamartoma, thrombosis of the splenic vein, reticuloendothelial invasion by lymphomatous processes, myeloid metaplasia, subacute and chronic infections such as tuberculosis, syphilis, brucellosis, or malaria, lipoidosis, sarcoidosis, lupus erythematosus, etc , cause identical degrees of splenic enlargement The absence of other evidences of liver disease facilitates differential diagnosis Biochemical tests, needle biopsy of the liver, percutaneous splenography, and hepatic vein catheterization are all helpful in eliminating hepatic disease Splenic puncture, using a # 20 needle and a 5 cc syringe, for aspiration may provide evidence for primary spleen involvement, particularly if lymphomas are present (10) We used the Vim Silverman needle for splenic biopsies in three instances but now recommend needle aspiration because of its safety and equal diagnostic value Occasionally it is difficult to determine the relationship between splenic and hepatic abnormalities Illustrative is a patient seen with jaundice, anemia, and an enlarged spleen Liver function studies showed an elevated bilirubin, low cholesterol esters, an elevated serum globulin, low serum albumin, and positive flocculation tests Needle biopsy of the liver revealed sinusoidal puddling of red blood cells and erythrophagocytosis The Coomb's test was positive A diagnosis of acquired hemolytic anemia was made. With adrenal steroid therapy all hepatic and hemolytic abnormalities disappeared temporarily

Splenomegaly has been extensively investigated in patients with heart disease It has been indicated that an enlarged spleen in chronic circulatory congestion suggests the presence of hepatic fibrosis Our studies show that this is true In patients with con-

It was not clear whether jaundice was due to the sickle cell disease, a superimposed viral hepatitis, or extrahepatic biliary obstruction. A heterophile antibody test for infectious mononucleosis was negative, and a gallbladder series done after the icterus had cleared was normal

	1947-1948 Before hepatitis	*1948 During hepatitis*	*1948-1951 After hepatitis*
Hepatomegaly	0	3+	0
Splenomegaly	0	0	0
Spider angiomas	0	0	0
Fibrosis	1+	4+	0
Fluid retention	0	0	0
Biochemical study			
RBC	2.8–4.0	3.3–2.8	2.4–4.0
Reticulocytes (%)	10	8	13
Sed rate hr. (Cutler)	6	22–2	2–5
Urine urobilinogen	1:30	1:1000–1:30	1:20–1:30
Urine bile	0	4+0	0
Serum bilirubin (mg %)	1.4–2.2	3.0–2.0	2.4–1.4
Serum alkaline phosphatase (B U)	4.8	6.8	3.4
Total serum cholesterol (mg %)	146	09–226	188–250
Cholesterol esters (mg.%)	64	26–180	113–141
Serum albumin (Gm %)	4.3	3.8	3.6
Serum globulin (Gm %)	3.2	4.5	4.3
Cephalin flocculation	2+	4+–1+	1+–2+
Thymol turbidity (units)	1.0	13–5.0	2–4.0
Histologic study			
Fibrosis	0	0	0
Fat	0	0	0
Regeneration	1+	1+	1+
Bile stasis	0	0	0
Infiltration	1+	2+	1+
Necrosis	0	1+	0
Other	Red cell stasis	Disarray of liver cells	Red cell stasis
Pathologic diagnosis	No significant abnormality	Viral hepatitis	No significant abnormality

Comment The recognition of viral hepatitis in the presence of preexisting hepatic disease is sometimes possible when clinical, biochemi-

tion of follicle stimulating hormone, endometrial atrophy, and low urinary estrogens Occasionally climacteric patients with liver disease have a normal or low level of urinary gonadotropin (FSH), endometrial hyperplasia, and increased urinary estrogens

Gynecomastia due to hepatic dysfunction must be differentiated from enlarged breasts encountered in testicular, pituitary, or adrenal disease where there is a concurrent liver disorder This condition occurs in roughly 10 per cent of patients with testicular neoplasms and is characteristic of individuals with idiopathic atrophy of the seminiferous tubules (Klinefelter's syndrome) (13) and eunuchoidism secondary to infections or trauma Hypoanterior pituitarism and estrogen-producing adrenal tumors are also *sometimes associated with gynecomastia In many instances, the* etiology is obscure Diagnosis is difficult when hepatic metastases are present in patients with testicular or adrenal neoplasms, and when intercurrent viral hepatitis or nutritional liver disease is present in congenital or degenerative endocrine diseases Hormonal assays are helpful when routine studies do not provide data for a specific diagnosis Klinefelter's syndrome is characterized by an elevated urinary FSH level in addition to azoospermia, small testes, and gynecomastia An elevated urinary LH occurs in chorioepithelioma, low urinary FSH is seen in hypopituitarism, and increased urinary pregnanediol may occur in feminizing adrenal tumors

LABORATORY ABNORMALITIES

The emphasis on laboratory study in clinical medicine has led to the widespread use of liver function tests in evaluating the role of the liver in systemic disease The nonspecific nature of available tests precludes their use alone as an indication of hepatic dysfunction, and it is necessary to establish criteria for interpreting abnormal results

An elevated serum bilirubin is the only specific test which localizes a lesion in the hepatobiliary system The bromsulfalein test is the next most reliable, however, its use in diagnosis is limited because of the influence of circulatory factors Other tests of

gestive heart failure, eight per cent of those with passive congestion without fibrosis of the liver had splenomegaly, whereas 11 per cent of those with centrilobular fibrosis and 33 per cent with diffuse fibrosis had an enlarged spleen (11)

ASCITES

Ascites is a nonspecific sign which is due to liver disease, but it occurs in various pathologic states where there is no grossly demonstrable hepatic injury Heart failure, kidney disease, tuberculous peritonitis, and neoplasms in the absence of hepatic injury are often accompanied by accumulation of peritoneal fluid Clinical findings and circulation tests provide helpful diagnostic data on patients with cardiac disease. Urinalysis and renal function tests permit clarification of the relationship of kidney disease to fluid retention Bacteriologic studies facilitate recognition of tuberculous peritonitis Analysis of ascitic fluid is helpful in differentiating abdominal fluid due to metastatic carcinoma from that due to liver disease Large macrophages and degenerated epithelial cells occur in ascitic fluid from patients with cirrhosis and may cause considerable difficulty in interpretation The protein and cell content of the fluid obtained from the peritoneum of patients with generalized carcinomatosis also helps in determining the etiology of ascites. The fluid is usually a transudate in cirrhosis and is often an exudate with abdominal carcinomatosis Ovarian fibromas which produce ascites and hydrothorax cause considerable diagnostic difficulty (12)

ENDOCRINE DISTURBANCES

Menopausal and postmenopausal women with liver disease may have uterine hemorrhage due to the influence of hepatic abnormalities on estrogen metabolism. It is necessary to differentiate these patients from those with neoplasms or pituitary–ovarian dysfunction who have pathologic bleeding Hormonal assays, cytologic studies, and endometrial biopsies are valuable in problem patients The menopause is characterized by increased excre-

capsule or interlobular septa with fibrotic processes This may lead to an erroneous diagnosis of hepatic fibrosis (18) A liver biopsy may be considered normal because the specimen in inadequate or does not contain disease localized to certain areas of the lobule. In these circumstances, clinical and biochemical findings should be relied on and the histologic study repeated until the clinician is satisfied that adequate material has been obtained

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liver function must be correlated with clinical findings to properly assess the influence of extrahepatic factors on reported results. Most systemic diseases are accompanied by abnormalities in plasma protein. Serum globulins are notably increased in Boeck's sarcoidosis, multiple myeloma, lymphopathia venereum, kala-azar, etc. Serum alkaline phosphatase, lipid partition, and carbohydrate studies are abnormal in many nonhepatic diseases. The serum alkaline phosphatase is increased in bone growth and a variety of bone lesions. Serum cholesterol depends upon the nutritional state, thyroid function, renal function, and inherent metabolic status, as well as the functional integrity of the liver. An abnormal glucose tolerance curve is frequently present in patients with liver disease and must be differentiated from that of latent or overt diabetes mellitus. The glucose tolerance test with simultaneous serum inorganic phosphorus determinations may be helpful in diagnosis.

Needle biopsy of the liver is of value in determining the significance of abnormal findings in liver function tests. There is no specific correlation of anatomy and a single battery of liver function tests in liver disease (14). However, identification of abnormal histology often establishes a basis for biochemical alterations.

Abnormal histology of the liver usually provides concrete evidence of hepatic disease. There are a variety of extrahepatic processes which can cause transient morphologic changes which may mislead the clinician. An attempt to interpret minimal changes in cell structure has been helpful in understanding the pathophysiology of liver disease, but such an approach has little clinical application with our present knowledge. In the past, a common error consisted in interpreting transient changes seen in biopsies obtained at surgery as an indication of a hepatic disorder. It is now evident that most surgical trauma will produce an inflammatory reaction which is transient and in no way reflects the basal state of the liver (15). Similarly, nonspecific changes which occur in systemic disease must be differentiated from those due to primary liver disease. A less common error is the confusion of connective tissue contained in the hepatic

6

GENERAL PRINCIPLES OF THERAPY

THE BASIC treatment of liver disease consists of (a) elimination of causative factors, (b) a judicious program of rest, (c) appropriate dietary therapy, and (d) management of secondary clinical complications. Discovery and treatment of etiologic factors is of first importance. Patients with nutritional deficiency due to alcoholism, systemic disease, or the unavailability of proper food, require an adequate dietary intake, psychologic rehabilitation to control alcoholism, and treatment of the disease processes which interfere with ingestion or assimilation of food. Cardiotherapy is necessary for congestive heart failure, surgery is essential for relief of extrahepatic biliary obstruction, and specific antibiotics and other drugs should be used whenever possible in patients with liver disease due to infectious and toxic agents. A combination of surgery, x-ray therapy, and chemotherapy may be beneficial in patients with primary or secondary neoplastic involvement of the liver.

Public health measures are necessary to control certain etiologic factors which cause hepatic disease. Proper disposal of feces of patients with viral hepatitis is essential to prevent pollution of water and food. Gamma globulin is desirable in debilitated persons or pregnant women exposed to viral hepatitis "I H." Preventive measures for viral hepatitis "S H." include avoiding pooled

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justification for employing rest regimens is based on the fact that physical activity increases energy needs and reduces hepatic blood flow (2) Exercise does not materially affect oxygenation of hepatic cells in normal subjects, or those with uncomplicated viral hepatitis or nutritional liver disease. However, patients with passive congestion of the liver due to heart failure have a marked reduction in oxygen saturation of hepatic venous blood with physical activity (3)

The most complete study of the effects of physical activity on acute hepatic disease was conducted by the Armed Forces Commission on Liver Diseases on troops in the Korean War. This comprehensive study led to the following recommendations for treatment of young persons with a mild form of viral hepatitis not complicated by other diseases (4)

1. Hospitalize patients with acute viral hepatitis as soon as feasible for physical activity to the point of fatigue may be harmful
2. Maintain bed rest as long as acute symptoms persist Once patients begin to feel well, regardless of the degree of jaundice, *they should not be forced to stay in bed* for more than one hour after each meal Restriction to the hospital ward is essential to prevent undue activity or exertion
3. Discharge patients from the hospital and initiate physical reconditioning after the total serum bilirubin is below 1 5 mg/100 ml, and the bromsulfalein retention in 45 minutes is below 6% for a period of not less than one week Patients whose bromsulfalein retention stabilizes between 5 and 10% may also be discharged from the hospital with safety
4. Patients should be followed up for two weeks with weekly physical examination, serum bilirubin, and bromsulfalein tests Recurrent abnormalities will occur rarely and are probably indications for rehospitalization

This program circumvented the usual delay required for recovery from the effects of prolonged rest in bed and shortened the period of hospitalization Earlier ambulation also prevents complications from bed rest such as phlebitis, pneumonia, and renal calculi A similar regimen has been used on patients seen in civilian practice without untoward effects Indeed, it has often

plasma, routine liver function tests on professional blood donors, and exclusive use of autoclaved needles and syringes. Similarly, other viral, bacterial and protozoal diseases and hepatotoxic chemical agents require special programs for prophylaxis.

In the Jersey City Medical Center, a program has been instituted for rehabilitating alcoholic patients with liver disease. A survey shows a significant reduction in morbidity and mortality from liver disease in chronic alcoholism (1). *Patients hospitalized for alcoholism and its complications have been routinely studied for the presence of liver disease. With its discovery, they are made aware of the necessity for control of hepatic abnormalities by dietary therapy and abstinence from alcohol. After initial studies, patients are discharged to a clinic for long-term follow-up. Clinic personnel consists of physicians, nurses, a dietitian, and a psychologist. The Public Health Nursing Service makes periodic visits to check the home environment. Ambulatory evaluation includes a review of adherence to treatment, physical examination, biochemical liver function tests, and psychologic testing. Patients are rehospitalized for needle biopsy at intervals depending on the previous pathologic findings. Those with marked emotional disturbances are referred to the Psychiatric Clinic.*

Ability to control alcoholism is related to the severity of the physical disability accompanying the liver disease and the psychologic status of the patient. In a series of 167 chronic alcoholic patients with liver disease, 45 per cent adhered to a regimen of abstinence from alcohol and maintenance of an adequate diet. This was associated with disappearance of all evidence of liver disease with a fatty liver and stabilization of the hepatic process with mild to moderate cirrhosis. Progressive clinical, biochemical, and histologic changes which terminated in irreversible hepatic insufficiency were noted in patients who did not adhere to therapy.

REST

The amount of rest required for patients with liver disease depends on the etiology and severity of the disease. The physiologic

liver injury (3). Strict bed rest is also indicated for patients with trauma of the liver until hemostasis has been effected and an adequate opportunity has been provided to eliminate the possibility of masked liver injury

DIET

Dietary therapy is an important part of the treatment for all types and degrees of liver disease Recovery can be delayed by inadequate attention to diet A successful therapeutic program depends upon provision of sufficient calories and adequate carbohydrate, protein, fat, mineral, and vitamin content (Table 7) Expert assistance from nutritionists and dietitians is desirable Patient education is necessary. The device of keeping a daily food diary is helpful to review amount of food actually eaten

Optimally, the diet for liver disease is adjusted to meet the needs of the patient Emphasis on food palatability is essential to insure its consumption by the most desperately ill patients Cognizance must be taken of previous dietary habits, and an attempt made to adjust diet prescriptions so that they are practical The average patient who has liver disease requires approximately 375 Gm. of carbohydrate, 130 Gm of protein, and 100 Gm of fat (Table 7)

Caloric requirements vary considerably It is desirable to maintain adequate food consumption for basal needs and anticipated activities At the same time, it is necessary to avoid excess calories Deficient caloric intake causes a drain on tissue energy stores and interferes with recovery, excess calories lead to obesity A good food intake is maintained to prevent negative nitrogen balance and loss of normal adipose tissue Patients who are unable to eat because of anorexia may be tube fed, or receive supplemental parenteral alimentation. Adrenal steroids are of value in increasing appetite, chlorpromazine is helpful in control of nausea and vomiting.

Obesity not infrequently results from injudicious use of high caloric diets in liver disease This is common in viral hepatitis where patients are given two to three times the number of calories

been difficult to restrict physical activity completely in patients under 25 years of age. We have had several patients who have had a serious relapse with early ambulation. It is safer to curtail activity until clinical and biochemical abnormalities have disappeared Complete rest in bed is not essential but exercise should be undertaken with care

Between two and three months are required for histologic abnormalities to disappear completely in patients with viral hepatitis. These changes often persist in the absence of clinical and biochemical alterations. Patients with morphologic changes may participate in normal work activities but should avoid major stress.

The program outlined for viral hepatitis can also be employed in liver injury due to other infective and toxic agents. No special regimen is required in uncomplicated biliary obstruction. Patients with fatty liver or mild nutritional cirrhosis respond well to early ambulation However, therapy to reduce the fat and curtail activity in the connective tissue stroma should be effective before permitting complete ambulation. Continued hospitalization insures good dietary habits, provides a longer period for inpatient psychotherapy, and documents the status of the liver at the end of therapy.

Clinical symptomatology should govern the degree of physical activity permitted patients with moderate to marked cirrhosis. Complete bed rest should be discouraged but physical activity ought to be restricted until clinical symptoms are absent and biochemical and histologic abnormalities are stabilized. Bed rest is indicated to control hepatic pain and tenderness, and is advisable for patients with icterus, sensorial changes, fetor, and fluid accumulation Marked retention of bromsulfalein, hypoalbuminemia, and low cholesterol esters, as well as necrosis or active inflammation on biopsy, are indications for restricted activity

Complete rest in bed is desirable for patients with acute passive congestion of the liver, and a modified rest program is recommended with persistent hepatomegaly in heart failure (5). Physical activity causes a reduction of splanchnic blood flow in patients with heart disease, and contributes to the evolution of chronic

liver injury (3). Strict bed rest is also indicated for patients with trauma of the liver until hemostasis has been effected and an adequate opportunity has been provided to eliminate the possibility of masked liver injury

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Caloric requirements vary considerably It is desirable to maintain adequate food consumption for basal needs and anticipated activities At the same time, it is necessary to avoid excess calories Deficient caloric intake causes a drain on tissue energy stores and interferes with recovery, excess calories lead to obesity A good food intake is maintained to prevent negative nitrogen balance and loss of normal adipose tissue Patients who are unable to eat because of anorexia may be tube fed, or receive supplemental parenteral alimentation Adrenal steroids are of value in increasing appetite, chlorpromazine is helpful in control of nausea and vomiting.

Obesity not infrequently results from injudicious use of high caloric diets in liver disease This is common in viral hepatitis where patients are given two to three times the number of calories

Table 7 Hepatic Diet (High protein, high carbohydrate, moderate fat, salt not restricted)

This diet is constructed to provide all of the essential amino acids and vitamins. It provides approximately 3000 calories with a minimum of 375 Gm of carbohydrate, 130 Gm of protein, and 100 Gm of fat.

BASIC CONSTITUENTS

Milk	1 quart whole milk
Meat, fish, poultry	2 servings, 6 oz.
or cottage cheese	5 tablespoons
Egg	2
Fruit	3 servings, 1 citrus
Vegetables	2 servings
Potato	1 serving
Cereal	2 servings
Bread, whole wheat	8 slices
Butter	if tolerated
Jelly	4 tablespoons

TYPE MENU

Breakfast	*Dinner*	*Supper*
Fruit juice–6 oz	Lean meat, fish or poultry–3 oz	Lean meat, fish, poultry or cottage cheese
Cereal–⅔ cup with milk and sugar	Potato–1 serving	Potatoes, noodles, rice or spaghetti
2 eggs	Vegetable–2 servings	Salad–no dressing
2 slices toast	2 slices whole wheat bread	Vegetables–2 servings
Jelly or preserves	Fruit or sherbert	2 slices whole wheat bread
Milk, coffee or tea with sugar and cream	Milk–1 glass	Jelly, butter
		Cake, fruit or gelatin
		Milk–1 glass, tea or coffee with sugar and cream

9 00 P.M.–2 slices whole wheat bread with cheese, butter or jelly. Milk–1 glass

required for maintaining body weight. Adiposity is associated with increased liver fat and further impairment of liver functional reserve. Patients with nutritional cirrhosis develop fat in parenchymal cells, impaired carbohydrate tolerance, or hypercholesterolemia when excess caloric intake is continued for long periods.

Utilization of carbohydrates may be impaired in liver disease

because of a disturbance of intracellular enzymes or coexistence of diabetes mellitus It is necessary to adjust carbohydrate intake in such patients. Extra intake is indicated in patients with poor glycogen stores or hepatogenic hypoglycemia, consumption should be restricted in diabetes Division of ingested starches into four or six small feedings facilitates control of blood sugar levels Sweetened drinks and hard candy may be used to supplement the carbohydrate content of regular feedings

Ingested protein should consist of an amount sufficient to maintain nitrogen equilibrium and at the same time avoid untoward effects of a high intake Animal protein which contains a larger number of essential amino acids, and vegetable protein with a somewhat lesser nutritive value should be included in the menu Protein feeding induces an increased splanchnic blood flow, splanchnic oxygen consumption, and arteriohepatic vein oxygen difference as compared with fasting levels in both normal and cirrhotic subjects (6) Large quantities of protein cannot be metabolized by a poorly functioning liver, and nitrogenous waste products accumulate to produce mental changes (7) Hepatic coma results from high protein intakes in patients with spontaneous or surgically induced porta caval shunts (8) High protein intake is associated with accelerated recovery in acute mild viral hepatitis (4), and is valuable in patients with body protein deficits resulting from chronic liver disease In most instances, increased protein feeding will not improve serum protein deficits unless there is simultaneous improvement in hepatic reserve

Fat content of the diet should be sufficient to provide palatability Normal fat contained in meat, eggs, and dairy products is acceptable if there is no bloating or gaseous eructation Increased consumption of fat may be helpful in patients with functional hypoglycemia, and decreased intake is desirable when there is maintained hyperlipemia or hypercholesterolemia

Dietary salt restriction is the most important method of preventing further sodium accumulation in patients with peripheral edema or ascites (9) In a series of 114 patients with moderate to severe nutritional cirrhosis observed in our clinic, reaccumulation of ascites was prevented in 72 (64 per cent) by stringent

Table 8. Average Sodium Content of Common Foods Allowed on Low-Sodium Diet
(Sodium mg./100 Gm. of food)

FRESH FRUITS			
Apples	0.2	Orange	0.3
Apricots, raw	0.6	Orange juice	0.5
Banana	0.5	Peach, raw less skin	0.5
Blackberries	0.2	Pear, raw less skin	2.0
Blueberries	0.6	Strawberries, raw	0.8
Cherries, dark	0.8	Raspberries	0.3
Grapefruit, fresh	0.5	Watermelon	0.3
Grape juice	1.0		
FRESH VEGETABLES			
Asparagus, tips	2.0	Lima beans	1.0
String beans	0.9	Rhubarb	1.0
Corn—milk stage	0.4	Squash, yellow, less rind	0.5
Peas	1.0	Pumpkin, less rind	0.6
Cucumber	0.9	Okra	1.0
Onions	1.0		
CEREALS			
Oatmeal	2.0	Rolled Oats	2.0
Puffed Rice	1.0	Cream of Wheat, plain	2.0
Instant Ralston	1.0	Shredded Wheat	2.0
MEAT AND FISH*			
Lean beef	51	Fresh cod	60
Turkey liver	51	Lean raw pork	58
Lean veal	48	Halibut, raw	56
Chicken breast	78	Duck, breast	68
MISCELLANEOUS			
Matzoth	1.0	Eggs	137.0
Salt free bread	3.0	Spry (vegetable shortening)	0.4
Milk, salt poor (Lanolac)	13.0	Regular dry coffee	2.0
Sweet butter		Pecan, raw	0.3
Honey	7.0	Peanuts, raw with skin	2.0

* By boiling and decanting water, one may reduce sodium content as desired, although taste is usually sacrificed.

control of sodium intake (Table 8). A low sodium diet lowers the serum sodium, and, thereby, induces diuresis by inhibiting the production of the pituitary antidiuretic hormone. On the other hand, a low sodium intake tends to prevent diuresis by stimulating release of adrenal salt retaining hormones. To correct abnormal

sodium retention, it is desirable to permit only that amount of sodium which is excreted without the influence of diuretics The therapist must be aware of the tolerance of a given low sodium diet and its effect on morale, general metabolic needs, and body electrolyte economy Requisites for an ideal low sodium diet will, therefore, include sufficiently low sodium, palatability, and adequate calories, minerals, and vitamins (10) Salt substitutes which improve taste are useful in patients who require long-term sodium restriction

Parenteral or tube feeding is required for patients who have marked anorexia, nausea, or vomiting Tube feeding is preferable for it is possible to supply all nutritional requirements by this route A soft or synthetic rubber tube which is nonirritating may be left in place for a period of several weeks Liquid formulas containing adequate calories, protein, carbohydrates, and fat may be given in divided doses every two hours to maintain nutritional balance (Table 9)

Table 9 High-Protein Mixture for Tube Feeding

	Quantity
Milk, whole, homogenized (1 quart)	975 cc
Liver, raw, ground	100 Gm
Cream, 20%	100 cc
Egg, 1 to 2	50 Gm
Skim milk powder	40 Gm
Sugar or Dextro-Maltose	200 Gm
Orange juice	150 cc
TOTAL	1,500 cc

Parenteral alimentation should be planned to provide a minimum number of calories along with adequate carbohydrates, vitamins, and minerals Carbohydrates may be provided by a mixture of glucose and fructose A much larger portion of administered fructose enters the liver cells than in the case of glucose (11), and there is a separate, specific set of hepatic enzymes for disposal of fructose The chief disadvantage of using fructose is that an injured liver may not be able to transform sufficient amounts of fructose to glucose to supply the needs of the brain and muscles (12).

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Table 10 Daily Therapeutic and Supplemental Vitamin Requirements in Adults

	Therapeutic	*Supplemental*	*Representative preparations*
Vitamin A	50,000 units	5,000 units	Oleo vitamin A U S P
Thiamine	10–20 mg	1 0–2 0 mg	Thiamin hydrochloride USP
Riboflavin	20–30 mg	2 0–3 0 mg	Riboflavin USP
Nicotinic acid	100–200 mg	10–20 mg	Nicotinic acid USP Nicotinic acid Amide USP
Pyridoxine	10 mg	2 0 mg	Pyridoxine hydrochloride USP
Folic acid	10–15 mg	0 1–0 2 mg	Folic acid USP
Choline	15–30 Gm by mouth	1 5–3 0 Gm	Choline gluconate NNR Choline chloride NNR Choline dihydrogen citrate N F
Pantothenic acid	Unknown	?5 0 mg	Calcium pantothenate
Biotin	Unknown	Unknown	Biotin
Ascorbic acid	1.0 Gm	75 mg	Ascorbic acid USP
Vitamin D	20,000–30,000 U	200–400 units	Cod liver oil USP Calciferol USP
Vitamin K	Oral 1 2 mgm Menodione I M 1–10 cc Hykinone I.M 75 mg Synkovite I V 50 mg Mephyton		Menodione, USP Menodine sod Bisulfite injection USP (Hykinone) Vitamin K_1 USP (Mephyton) Sodium menadiol Dephosphate NNR Synkovite
Vitamin E	100–250 mg ?	30 mg ?	Alpha tocopherol

tained in the diet or in the form of vitamin supplements Excess vitamin dosage is discouraged because of waste and the possibility of inducing hypervitaminosis syndromes Hypervitaminosis A, characterized by hepatosplenomegaly, anemia, and bone altera-

Intravenous protein hydrolysates have been well tolerated and improved nitrogen balance in selected patients with moderate liver injury (13) They should not be used with acute or severe liver disease since they cannot be metabolized and may precipitate sensorial changes In addition, nausea and vomiting, hyperpyrexia, or anaphylactic reactions may occur when the rate of injection or concentration is too great Protein hydrolysates are given in 5 per cent solutions at a rate not exceeding 25 Gm./hour. Available preparations include hydrolysates of bovine blood plasma (Travamin), and protein hydrolysates (Aminosol, hyprotigen, Amigen, and Parenamine). Human salt-poor albumin is the protein of choice for parenteral therapy in patients with hypoalbuminemia It is given in doses of 2 units each day until the desired plasma albumin content has been obtained (14). Repeated transfusions of packed red blood cells has been advocated as another source of protein (15). However, with marked degrees of hepatic dysfunction such therapy frequently causes icterus.

Emulsions of fats have been used in the laboratory and to a limited extent in clinical research. Further technical improvements which facilitate preparation of a stable emulsion and reduce dangers of embolization may make this a practical form of therapy.

Vitamin Therapy

Vitamin deficiencies are frequently seen in patients because of inadequate intake, disturbance of absorption, or increased destruction, utilization, or excretion Decreased absorption of the fat soluble vitamins A, D, K, and E regularly occurs in biliary obstruction and parenchymal disease accompanied by jaundice Deficient intake of vitamin C and members of the vitamin B complex is notable in patients with nutritional liver diseases Tissue catabolism in both acute and chronic hepatic disease causes negative vitamin balance

Therapeutic quantities of vitamins should be given orally or parenterally in patients exhibiting symptoms of hypovitaminosis (Table 10) High intakes are frequently required for periods of several weeks and should be followed by moderate intake con-

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Nicotinic acid	100–200 mg	10–20 mg	Nicotinic acid USP Nicotinic acid Amide USP
Pyridoxine	10 mg	2 0 mg	Pyridoxine hydrochloride USP
Folic acid	10–15 mg	0 1–0 2 mg	Folic acid USP
Choline	15–30 Gm by mouth	1 5–3 0 Gm	Choline gluconate NNR Choline chloride NNR Choline dihydrogen citrate N F
Pantothenic acid	Unknown	?5 0 mg	Calcium pantothenate
Biotin	Unknown	Unknown	Biotin
Ascorbic acid	1 0 Gm	75 mg	Ascorbic acid USP
Vitamin D	20,000–30,000 U	200–400 units	Cod liver oil USP Calciferol USP
Vitamin K	Oral 1 2 mgm Menodione I M 1–10 cc Hykinone I M 75 mg Synkovite I V 50 mg Mephyton		Menodione, USP Menodine sod Bisulfite injection USP (Hykinone) Vitamin K_1 USP (Mephyton) Sodium menadiol Dephosphate NNR Synkovite
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tained in the diet or in the form of vitamin supplements Excess vitamin dosage is discouraged because of waste and the possibility of inducing hypervitaminosis syndromes Hypervitaminosis A, characterized by hepatosplenomegaly, anemia, and bone altera-

tions (16), and hypervitaminosis D causing generalized calcific deposits (17), develop with prolonged and excessive use of vitamins A and D, respectively.

SEDATIVES AND ANALGESICS

Patients with mild to moderate impairment of hepatic reserve *tolerate sedatives and analgesics without difficulty. The liver retains its ability to detoxify* the commonly employed soporifics and *hypnotics until late in the course of liver disease. Studies of* barbiturate tolerance in hepatic disease *show no increased sensitivity or delay in excretion* (18). *Paraldehyde and chloral hydrate* are also well tolerated. In our experience, subjecting patients in this category to general anesthesia with *morphine sulfate as a* preanesthetic agent has not been associated with untoward effects. Tranquilizing agents such as meprobamate, reserpine, and chlorpromazine are well tolerated and have been useful in therapy of alcoholics with hepatic abnormalities. Although chlorpromazine is hepatotoxic, in the absence of sensitivity reactions no ill effects have been seen in patients with established liver disease.

Choice of a sedative in patients *with severe hepatic dysfunction* constitutes a major problem. Use of any central nervous system depressant may increase clouding of mental faculties or precipitate coma. None of the present drugs is satisfactory for they all depend partly on the liver for disposal. In selecting a sedative or analgesic in the presence of terminal liver disease, the physician must consider its time of onset of action, fate, rate of excretion and tolerance in relation to needs of the patient.

CATHARTICS

Constipation which is often prominent in patients with liver disease may be due to disturbance of bile metabolism, type of food ingested, and/or restricted activity. Mild catharsis is desirable. One of the normal functions of bile salts is to stimulate movements of the intestine. This has led to the use of bile in the treatment of constipation. Dehydrocholic acid promotes a free

flow of bile into the intestine thus facilitating physiologic laxation. This action is useful in the treatment of chronic constipation due to hepatobiliary dysfunction

Purgation should be avoided in patients with liver disease except with drug or food poisoning. The timing of administration of a cathartic should be such as to permit normal absorption of ingested food Emollient cathartics are desirable in patients with hemorrhoids and esophageal varices to prevent straining at the stool. Bulk cathartics are preferable for constipation which results from bed rest or physical inactivity. Occasionally, it is desirable to supplement these agents with an irritant cathartic to facilitate desired action and at the same time avoid the undesirable effects of both types of preparation

BILE THERAPY

Therapeutic agents which increase the volume of bile secretion (hydrochloretics), accelerate bile flow (chloretics), or cause gallbladder contraction (cholagogues) are occasionally desirable in patients with hepatobiliary disorders Hydrochloretics are of greatest practical value Dehydrocholic acid* is the most effective hydrocholeretic It promotes an abundant flow of dilute bile This facilitates transport of bile into the small intestine Hydrocholeresis counteracts the development of biliary stasis and its sequalae as seen in such conditions as chronic cholecystitis and cholangitis with incomplete biliary obstruction Dehydrocholic acid is useful for flushing the biliary tree to remove inspissated bile, small nonobstructing calculi and other detritus in selected patients This drug in combination with an anticholinergic agent such as homatropine methylbromide has been employed in the management of biliary dyskinesia

CORTICOTROPIN AND ADRENAL STEROIDS

Corticotropin and adrenal steroids are of considerable value in selected patients with liver disease Indication for these drugs

* (The pure oxidized bile acid is available as Cholan DH)

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includes cholangiolitic hepatitis with persistent elevation of serum bilirubin (19), fulminant hepatitis (20), hypoglycemia or glycogen storage deficits refractory to usual measures, some instances of hepatic coma, hemolytic reactions (21), and the presence of other diseases for which these drugs are of proven value (22).

Corticotropin, hydrocortisone, prednisolone, or one of the many other adrenal steroids may be given. The therapist must be constantly aware of the need for prescribing adequate amounts of these hormones, and at the same time employ measures to prevent complications.

It is desirable to evaluate adrenal function of the patient prior, during, and following the use of corticotropin and adrenal steroids. Three basic types of activity occur with adrenal steroid therapy: salt and water retention due to aldosterone effects (23), protein and carbohydrate metabolic effects and anti-inflammatory action due to glucocorticoids (22) and nitrogen retention due to androgenic and nonandrogenic 19 carbon compounds (24). It is possible to assay the salt and water hormone effects by measuring the concentration of sodium and chloride in the sweat, saliva, or urine, or evaluating the capacity to handle large amounts of water except in patients with fluid retention due to liver disease. Specific assay of glucocorticoid activity is accomplished by measuring serum levels or urinary excretion of 17-hydroxycorticosteroids, and eosinophile response to ACTH. Urinary excretion of ketosteroids reflects the functional status of the "N" hormone of the adrenal. The best measure of adrenocortical reserve is provided by giving 25 units of ACTH by an intravenous infusion during an eight-hour period and noting the increase of 17-ketosteroids or 17-hydroxycorticosteroids. Patients already receiving adrenal steroids may be studied by substituting 1 mg. of fluorohydrocortisone for each 25 mg. of cortisone and by conducting the assay as usual.

Complications of corticotropin or adrenal steroids often occur which are related to the physiologic activities of these drugs. Short-term complications include electrolyte disturbances, negative nitrogen balance, diabetes, a decreased inflammatory response, adrenal insufficiency, peptic ulceration, psychiatric

aberration, and poor wound healing Long-term side-effects consist of hypercholesterolemia, fatty liver, osteoporosis, polycythemia, hypertension, and virilism. These complications are minimized by limiting the amount of drug therapy and employing measures to decrease the intensity of adverse reactions A low-sodium, high-potassium, high-protein diet is desirable Testosterone, antacids, and antispasmodics may be helpful Prednisolone or adrenal steroids which have only minimal sodium binding properties should be used to prevent salt retention The clinician must recognize and treat serum potassium changes on an emergency basis A low potassium level and alkalosis should be treated with oral or intravenous potassium Of equal importance is the recognition and treatment of an elevated serum potassium Testosterone will interrupt protein catabolism and should be given to patients receiving long-term adrenal steroid therapy Continuous antacid and antispasmodic drug therapy is necessary to prevent peptic ulceration

Choice of ACTH or one of the available adrenal steroids depends upon whether the adrenal gland is intact and the desired speed of action It is often desirable to give a combination of corticotropin and adrenal steroids to prevent adrenal atrophy Aldosterone should be used when there is electrolyte depletion Prednisolone which has approximately four to five times the activity of hydrocortisone is the preparation of choice where a rapid and intense metabolic hormone effect is necessary In discontinuing adrenal steroids, adrenal dysfunction is prevented by giving corticotropin for several days to hasten recovery from corticosteroid depression This is particularly important when many homeostatic adjustments are deranged and reactions to stress may be impaired

FLUID RETENTION

Fluid accumulation in liver disease has been attributed to a combination of (a) excessive tubular reabsorption of sodium, secondary to failure to deactivate antidiuretic hormone or adrenal overactivity, (b) protein deficits causing a decrease in colloid

osmotic pressure, (c) increased hydrostatic pressure due to portal and hepatic vein hypertension, and (d) abnormal lymphatic drainage. The therapist may control sodium and protein balance when they are responsible for fluid retention and indirectly influence hydrostatic pressure and lymphatic drainage.

The value of sodium restriction has been discussed under dietary management. Resins may be helpful as an adjunct to sodium restriction. They permit a higher ingestion of salt and often induce a diuresis by their effect on other electrolytes. In our experience, they are poorly tolerated by one half of the patients receiving them. Untoward effects include gastrointestinal disturbances, acidosis, ammonium toxicity, and electrolyte deficiencies. Frequent laboratory study of plasma electrolytes is necessary. Ammonium resins should be avoided since they may cause apathy, weakness, disorientation, confusion, and electroencephalographic changes (25).

The average patient with hepatic insufficiency should be permitted a free fluid intake (26). Increased fluids are desirable in patients with sepsis or other disease processes which cause an excessive loss of body water. On the other hand, there is a marked intolerance to water in some patients with liver disease and restriction of fluids is necessary in this group. The ability to excrete ingested water should be evaluated, particularly in patients with fluid retention refractory to therapy. A simple test consists of giving 1000 ml. of 5 per cent glucose in water by vein over a 30-minute period and collecting all urine which is voided during the succeeding four-hour period. Normally, 1000 ml. or more of urine is excreted during four hours. Well hydrated patients with liver disease who excrete less than one half of infused water during the period of study should be maintained on a restricted water intake until their tolerance improves.

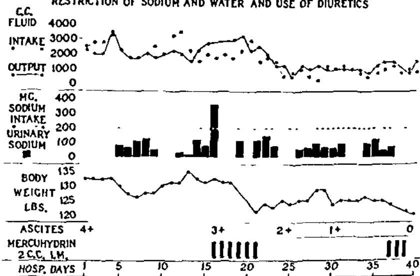
A trial period of diuretics is desirable with marked fluid retention in liver disease. Mercurials are the most potent available diuretics; oral as well as parenteral preparations are available. *Systemic mercurials are the preparations of choice where speed or a large diuresis is desired.* Intramuscular or subcutaneous mercurial diuretics should be used in doses of 1–2 cc. each day for

a period of two to three days to assay their effectiveness They should not be given indefinitely if there is no response Oral mercurials may be valuable when slow, smaller diuretic effects are wanted (27) (Fig 24a)

In selected patients, acidifying salts, xanthines, and Diamox may be useful adjuncts to mercurial diuretics, or can be used alone where a small diuresis is desired Ammonium chloride is particularly helpful in potentiating mercurials and prevents the development of hypochloremic alkalosis occasionally seen with vigorous diuretic therapy. In large doses or with decreased renal reserve it tends to induce hyperchloremic acidosis (28), and with severe hepatic dysfunction it causes ammonium toxicity (25) Theophylline derivative and Diamox are sometimes of value in patients with minor electrolyte disturbances causing temporary refractoriness to diuresis A copious diuresis has occasionally resulted following a short period of therapy with these drugs Diamox depresses the sensorium and its use in patients with marked hepatic insufficiency may precipitate coma (29)

Careful attention to protein balance is helpful Correction of hypoalbuminemia may interrupt the cycle of fluid retention Oral protein will rarely increase plasma albumin, and salt-poor albumin in adequate doses is necessary Infusion of serum albumin is accompanied by a temporary antidiuresis This has been attributed to activation of the osmoreceptors and a specific effect on tubular reabsorption The antidiuresis may lead to acute lung edema (14b) We have not encountered ill effects when serum albumin in small doses is used over long periods of time in patients with hepatic disease and congestive heart failure refractory to therapy Dramatic diuretic effects are often obtained (Fig 24) It is our feeling that all patients with fluid retention associated with a normal hemoglobin mass and hypoalbuminemia should receive salt-poor albumin to determine its effectiveness Many patients respond with a good diuresis, others fail to improve because of additional factors which cause salt and water retention

Abdominal paracentesis and thoracentesis should be reserved for diagnostic study or relief of discomfort and dyspnea The following program for patients with fluid retention refractory to



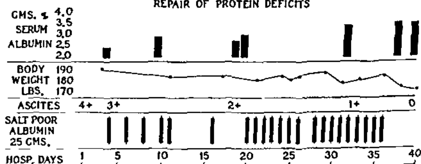


FIG. 24 Mobilization of fluid in nutritional cirrhosis with mercurial diuretics and sodium restriction (*top*) and with salt-poor albumin (*bottom*).

therapy has permitted control of fluid accumulation in 60 per cent of patients with hepatic cirrhosis.

1 Laboratory data
   a. Daily weight, fluid, and sodium intake and output.
   b. Hematocrit, plasma volume, serum albumin and globulin, serum sodium, and potassium

2 Therapy
   a Correct anemia with transfusions of whole blood or pooled red blood cells depending on plasma volume.
   b Observe fluctuation of weight on a 200 mg sodium, 350 gm carbohydrate, 125 gm protein, and 100 gm fat diet, with fluids ad libitum
   c Use mercurial diuretics and assay effect
   d With failure to obtain a diuresis, reduce dietary sodium and water intake to amount excreted
   e Give salt-poor albumin if total circulating albumin (conc. × plasma vol) remains below 1 4 gm/kilo despite normal hematocrit
   f. Perform paracentesis if ascites is a source of marked discomfort or interferes with respiration

Paracentesis

EQUIPMENT

1 Alcohol
2 Iodine or other suitable antiseptic
3 Sterile towels
4 A 2 cc syringe
5 One hypodermic needle and a #24 2-inch needle
6 Procaine hydrochloride
7 Paracentesis trocar
8 Three test tubes
9 Skin clips, needles, catgut
10 Scalpel, Bard-Parker blade
11. Sterile gauze
12 Abdominal binder

TECHNIC

1 Support the patient in a sitting position.
2 Empty the urinary bladder by catheter.
3. Select a site for puncture that is between the umbilicus and the symphysis pubis near the midline, but at least one inch away from any surgical scar or previous paracentesis scar.
4 Prepare the skin with antiseptic agent Place sterile towels around the operative field
5 Anesthetize the skin, subcutaneous tissue, muscle, and peritoneum with procaine

6 Nick the skin with scalpel and introduce the trocar.
7 Permit all of the fluid to drain through the trocar. An electrical suction pump is inadvisable, it withdraws fluid too rapidly.
8 Approximate the skin with clips Continued drainage is inadvisable except when inadequate fluid has been obtained due to loculation Continuous drainage causes skin maceration, increases the risk of infection, and interferes with accurate recording of fluid losses
9 Apply a tight abdominal binder for 24 hours.

COMPLICATIONS

1 *Puncture of major blood vessels* This complication is often unavoidable With profuse or continued bleeding, surgical intervention may be necessary
2 *Puncture of intestines* This occurs in patients with previous abdominal surgery or numerous paracenteses when the trocar is introduced in an area where the intestines are bound to the anterior peritoneum
3 *Bladder puncture* This complication does not occur if each patient is catheterized prior to paracentesis.
4 *Peritonitis* Peritoneal infection results from faulty technics and is avoided with proper antisepsis
5 *Peritoneal shock* Severe pain accompanying entry into the peritoneal cavity may produce a shock-like state
6 *Salt and potassium depletion syndrome* The concentration of serum sodium, potassium, chloride, and protein decreases within a period of 12–24 hours after paracentesis This is due to the reestablishment of an equilibrium between the plasma and peritoneal areas Lowering of serum electrolytes precipitates hepatic coma in patients with severe liver insufficiency Maintenance of normal osmolarity of the plasma by infusion of salt-poor albumin after paracentesis prevents these electrolyte disturbances.

ELECTROLYTE DISTURBANCES

Diuretic therapy is often complicated by alterations of body sodium and potassium (30). Many patients have decreased serum concentration of these ions prior to receipt of any therapy. This has been attributed to hemodilution, hypercholesterolemia, and/or a readjustment of homeostatic mechanisms which control concen-

tration and distribution of sodium and potassium Increased concentration of sodium may be seen with salt intoxication or water dehydration, elevated potassium is present in patients who have renal functional impairment or are receiving intravenous potassium Estimation of total circulating sodium is desirable to interpret alterations in concentration of serum sodium Furthermore, this procedure allows one to recognize plasma sodium depletion in the presence of a normal serum concentration (31). Electrocardiographic studies constitute the simplest method of evaluating the significance of serum potassium alterations

Decreased circulating sodium is accompanied by weakness, hypotension, oliguria, and azotemia, elevated serum sodium content is accompanied by signs of water intoxication Treatment of sodium alterations requires individual attention (Table 11).

Table 11 Indicated Therapy with Alterations of Total Circulating Sodium

Total circulating sodium	*Serum sodium concentration*	*Plasma volume*	*Therapy*
Increased	Normal	Increased	Sodium restriction
Increased	Increased	Normal	Sodium restriction
Increased	Increased	Increased	Sodium restriction
Decreased	Normal	Decreased	Hypotonic saline
Decreased	Decreased	Normal	Hypertonic saline
Decreased	Decreased	Decreased	Isotonic saline
Normal	Increased	Decreased	Increased water
Normal	Decreased	Increased	Restrict water

Therapy of salt depletion depends on whether there is a concomitant loss of water Salt plus water loss is best treated by parenteral hypotonic saline Hyponatremia, due to hemodilution, requires restriction of fluid intake (Table 12) The classic salt depletion syndrome where there is a normal plasma volume and reduced concentration of sodium should be treated by infusions of 3 per cent sodium chloride (Table 12) Salt intoxication syndromes require restricted salt and water intake Hypernatremia due to water dehydration is best treated by increased fluid intake

Table 12 Influence of Therapy on Abnormal Serum Sodium Patterns in Severe Nutritional Cirrhosis

		Case A L	*Case J.*
CLINICAL FEATURES		Hepatic coma	Fluid retention refractory to treatment
TREATMENT GIVEN		Hypertonic saline	Water restriction
CLINICAL RESULTS		Hepatic coma disappeared	Fluid mobilized and hyponatremia controlled
LABORATORY RESULTS			
Plasma vol /Kg. bodyweight	B*	32 2 ml.	66 0 ml
	A*	42 3 ml	56 4 ml.
Serum sodium	B	118 8 mEq /100 cc.	127.6 mEq /100 cc.
	A	141 8 mEq /100 cc.	138 0 mEq /100 cc.
Total circulating sodium Kg.	B	3 7 mEq	8 7 mEq.
	A	6 0 mEq	7.7 mEq.
Potassium concentration	B	5 0 mEq /100 cc.	4 0 mEq /100 cc
	A	5 0 mEq /100 cc.	4 1 mEq /100 cc.
Chloride concentration	B	91 4 mEq /100 cc	100 mEq./100 cc.
	A	103 mEq /100 cc	101 mEq./100 cc.
Hematocrit	B	42%	37 4%
	A	41%	37 8%
Protein	B	16 5 mEq /100 cc	12.4 mEq /100 cc
	A	16 5 mEq /100 cc	13.1 mEq /100 cc.
Twenty-four hour urine sodium	B	25 mEq /100 cc	150 mEq /100 cc
	A	60 mEq /100 cc	156 mEq /100 cc

* B–Before therapy
* A–After therapy

Body potassium disturbances are characterized by muscular weakness, respiratory difficulty, lethargy, and abdominal distention. Potassium deficits should be corrected by oral replacement therapy whenever possible, and glucose infusions, intravenous calcium and/or artificial dialysis should be used to reduce marked elevations of serum potassium (32).

Magnesium deficiency may be responsible for tremor or delirium in hepatic cirrhosis Ammonium salts appear to be more toxic in patients with low serum magnesium levels. Deficits

should be corrected with 5 to 10 gm of magnesium sulfate given intramuscularly in 3 to 5 divided doses over a 24-hour period

HEMATEMESIS

Hematemesis in liver disease occurs from ruptured esophageal or gastric varices, bleeding peptic ulcer, gastritis, neoplasm, or other nonhepatic mechanisms which cause gastrointestinal hemorrhage Ruptured varices constitute the most common cause of hematemesis Numerous methods have been advocated for control of bleeding which results from a combination of sudden increase in venous pressure, ulceration, or errosion and or abnormalities in clotting potential

Palmer advocates immediate esophagoscopic evaluation and use of an Oxycel pack to effect local pressure and hemostasis (33) Packing is placed around a large gastric tube to prevent emesis Patterson has injected a sclerosing solution into the varix which is actively bleeding (34) Balloon tamponade is the most effective method for control of varix hemorrhage in the absence of a skilled esophagoscopist (35) Direct surgical ligation of varices is indicated when it is not possible to control hemorrhage by these methods (36)

Of equal importance is attention to abnormalities in hematemesis which include increased capillary fragility, hypoprothrombinemia, and platelet deficiency A high vitamin C and P intake and adrenal steroids may be helpful in patients with marked increase in capillary fragility Hypoprothrombinemia and platelet deficiency are best treated by fresh whole-blood transfusions now facilitated by the availability of plastic bags

The following program designed to replace blood loss, treat hemostatic defects, and mechanically control bleeding, has been effective in 60 per cent of our patients

1 Insert esophageal-gastric tube for balloon tamponage.
2 Type and cross-match blood Give fresh whole blood transfusions rapidly until shock disappears A cutdown should be performed and an indwelling siliconized needle inserted to permit continuous

transfusion Blood should be administered under pressure when there is shock or hypotension

3 Vitamins C, P, and K (Hemocoavit) has been given intravenously with evidence of increased capillary fragility and hypoprothrombinemia Prednisone or prednisolone are desirable for patients with platelet deficiency accompanied by purpura.

4 Restless patients may be given long-acting barbiturates for sedation

5 When it is not possible to control bleeding, esophagoscopy should be performed and followed by surgical ligation of varices.

Balloon Tamponage

EQUIPMENT

1 Sengstaken double-balloon tube (Fig 25).
2 Mercury manometer or aneroid gauge of the Tycos sphygmomanometer connected with a four-inch glass tube to upper balloon
3 50 cc. syringe
4 Intestinal suction machine
5 Lubricating jelly
6 Glass of water with straw
7 Hemostat for rubber tubing
8 Thrombin

TECHNIC [Adopted from Blakemore (35) and Linton (36)].

1 Elevate head of bed
2 Coat lower part of the tube and balloon with lubricating jelly and thrombin
3 Spray nostrils of patient and the posterior pharynx with butacaine until gag reflex is depressed
4. Insert tube through the nostril or mouth until the tip is in the posterior pharynx Then with swallows of water, pass the tube to the 50 cm. mark Inflate lower balloon with 100–200 cc. of air *and withdraw tube until resistance is encountered.* Place traction of 3–5 pounds on tube to maintain in place and compress gastric vessels Tape tube to nose Inflate upper sausage balloon to 20 ml of mercury pressure. This pressure will require approximately 40–60 cc. of air.
5. Aspirate stomach to remove blood, air, and swallowed water. Irrigate gastric tube with water to keep clear

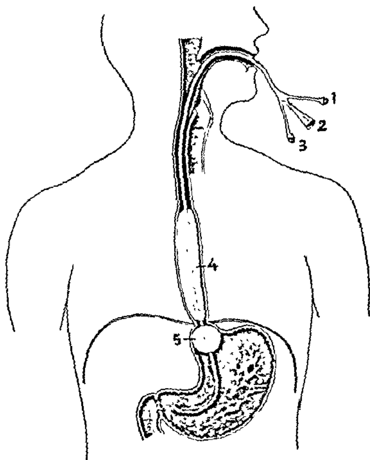


Fig. 25 Sengstaken tube for balloon tamponage 1. air inlet for esophageal balloon 2. gastric aspiration 3. air inlet for gastric balloon, 4, esophageal balloon, 5. gastric balloon

6 Adjust traction on stomach balloon and pressure in esophageal balloon until bleeding ceases When the esophageal balloon is in the proper position, the pressure will vary with the cardiac and respiratory cycles The pressure should not fall below 20-25 ml. of mercury
7 Clasp the branch of the "Y" tube used to inflate the esophageal balloon so that it will not leak air Check the pressure frequently for possible leakage
8 Connect the stomach tube to a suction machine and irrigate with 40 ml of warm saline every one-half hour. Use oral suction to remove saliva and other secretions
9 Give small amounts of thrombin solution by mouth when the balloon system is intact Keep the tube in place for a minimum of 24 hours Deflate to see if new bleeding occurs.
10 Keep patient hydrated and nourished with parenteral fluids
11 After withdrawing the tube, give the patient clear fluids and slowly advance to a soft diet

Balloon tamponage is effective only in instances of hemorrhage from an esophageal varix. Complications which occur with its use include: (a) regurgitation of the tube, (b) pressure necrosis of the esophageal mucosa, (c) clogging of the stomach tube to interefere with stomach aspiration, and (d) pulmonary aspiration of regurgitated or swallowed material.

In a study of 57 cirrhotic patients treated for bleeding esophageal varices in the Jersey City Medical Center, 24 succumbed during the initial attack of bleeding and 35 survived an episode of hemorrhage Each of the patients who succumbed to their first episode of esophageal hemorrhage had severe liver disease with general bleeding tendencies and/or marked biochemical dysfunction Shock due to blood loss was responsible for 13 deaths and hepatic coma for 11 deaths. Of the 33 patients with nutritional cirrhosis who survived an episode of bleeding varices, 11 were living one to eight years later, 6 were lost to follow-up, and 16 died within 3 months to 8 years after the initial hemorrhage Eight of these patients died of hepatic coma, three of recurrent hemorrhage, one of postoperative shock, and four of general debility.

A therapeutic program designed to improve hepatic reserve and

reduce gastric acidity is of great importance after bleeding has been controlled. This program may be used indefinitely as prophylactic therapy of varices.

1. Rest
2. Bland high carbohydrate, high protein, moderate fat diet
3. Supplemental vitamins including K and C
4. Antacids four times daily between meals in appropriate dosage
5. Propanthelne, tincture of belladonna, or other antispasmodic in appropriate dosage four times daily, before meals and at bedtime

Diagnostic procedures should be undertaken in patients with bleeding esophageal varices during convalescence to evaluate the need for further therapy.

1. Repeat liver function tests and needle biopsy of the liver
2. Esophagram and esophagoscopy
3. Prothrombin time, prothrombin consumption time, capillary fragility, platelet count, and bleeding and clotting time
4. Plasma volume, hematocrit

• Considerable study has been directed to the role of surgery in the control of bleeding varices in cirrhosis (37). The experiments of Madden and associates (38) show that numerous extrahepatic vascular shunts are present in the advanced stages of cirrhosis. These observations, coupled with the established role of peptic ulceration and hemorrhagic tendencies in bleeding esophageal varices, along with disappearance of varices in some instances after medical therapy (39), all indicate the necessity for careful selection of patients for surgical procedures.

Knowledge of approximate portal pressure as determined by the wedged hepatic vein pressure (40) or esophageal vein pressure (41) may be helpful in assessing the need for portal decompression. Clinical findings, biochemical reserve, and connective tissue activity and vascularity on needle biopsy should also be evaluated. Contraindications to surgery include: deep jaundice, hepatic fetor, sensorial changes, overt bleeding tendencies, hypoalbuminemia, marked bromsulfalein retention, a 4 plus cephalin flocculation, and histologic evidence of active necrosis or inflammation. In the absence of these clinical and laboratory evidences

of marked hepatic insufficiency, activity in the connective tissue stroma may be an indication for prolonged medical management. Nine patients with moderate active nutritional cirrhosis and bleeding esophageal varices observed in our clinic did not have repeat hemorrhage on medical therapy over a five-year period. A review of the case histories of this group gives the impression that improvement in morphology may facilitate intrahepatic circulation and, thereby, reduce portal hypertension. Serial studies of wedged hepatic vein pressure are being conducted to evaluate the effects of prolonged medical therapy on elevated portal pressure. Where portal hypertension is partly related to connective tissue and liver cell activity, improvement may result, however, when nodular regeneration of parenchymal cells is solely responsible for altered circulation, surgical portal decompression is required. Spontaneous development of new collaterals, prevention of ulceration from acid factors, and maintenance of a normal coagulation potential are of individual and collective importance in preventing recurrence of hemorrhage.

SURGICAL PROCEDURES FOR ESOPHAGEAL VARICES

A variety of surgical procedures have been recommended for treatment of esophageal varices. These procedures are of three general types, those which (a) obliterate the varices (b) improve collateral circulation, and (c) reduce portal hypertension. Esophageal veins may be obliterated by injecting sclerosing agents into these veins, by direct ligation or resection of esophageal veins, or by ligation of the coronary veins of the stomach. Both injection and direct ligation have been valuable in control of hemorrhage on an emergency basis. Resection of the veins, gastrectomy, and ligation of the coronary veins of the stomach have been used as definitive measures but have not been successful in preventing recurrence of hemorrhage.

Omentopexy and surgical production of a mediastinitis have been proposed as means to increase collateral circulation and reduce portal hypertension. Recently, a procedure called hepatopexy, in which magnesium trisilicate powder is applied to

abraded areas on the superior surface of the liver and to the inferior surface of the diaphragm, has been advocated to increase the vascular bed of the outflow tract of the liver (38).

Surgical approaches which directly reduce portal vein pressure include portacaval shunts, splenorenal shunts, and ligation of the hepatic, splenic, and left gastric arteries Elevation of the portal venous pressure can be determined by hepatic vein catheterization or transesophagoscopic puncture of varices There is a normal gradient of 8–10 mm Hg in the hepatic vein, and a normal mean sinusoidal pressure of 5 mm Hg (40) The normal esophageal venous pressure is about 2–5 mm Hg (41) Decompression procedures are most helpful in cirrhotic patients who have an elevation of the mean sinusoidal pressure to 20–30 mm Hg and of the esophageal vein pressure to 12 20 mm Hg

Sclerosing Procedures (33)

Rationale

Obliteration of submucosal esophageal varices to reduce probability of later hemorrhage

Indications

a Recurrent hemorrhage from varices following portal decompression.

b Patients whose physical state does not permit more radical procedures

Contraindications

The presence of gastric varices Sclerosis of esophageal varices tends to increase pressure in gastric varices and predispose to their rupture Gastroscopic examination is, therefore, necessary for all patients before undertaking sclerosis of esophageal varices as a definitive measure

Technic

The Eder needle is used in conjunction with an esophagoscope and 1% Sotradecol or a 5% solution of sodium morrhuate is injected into each varix The procedure should be done in steps over a period of several weeks, a few varices being injected each time

COMPLICATIONS

a. Accentuation of gastric varices.
b. Production of a slough or stenosis of the esophagus.

Direct Suture of Esophageal Varices (36)

RATIONALE

Control of hemorrhage during emergency.

INDICATIONS

a. Continuous hemorrhage not controlled by balloon tamponade.
b. Repeated hemorrhage where general physical condition of the patient is too poor to withstand other operative procedure.

TECHNIC

a. A balloon tube is inserted to control bleeding.
b. Under general anesthesia (cyclopropane) the left pleural space is entered by resecting the seventh rib. The diaphragm is opened for a short distance at the esophageal hiatus.
c. A 5–6 cm. longitudinal incision is made in the esophagus and the cardia of the stomach. This exposes the esophageal varices.
d. The varices are picked up with mucosa covering them and sutured with #00 chromic catgut, using an intestinal atraumatic needle. The suture should pass through the mucosa and beneath the varix. It should extend from the gastric mucosa up the esophagus for a distance of 5–6 cm.
e. The incision in the esophagus and cardia is closed in a transverse manner, using three rows of interrupted fine silk sutures. The chest incision is sutured in a routine manner, and the pleural space drained with a catheter which is removed in 48 hours. Penicillin and streptomycin are given preoperatively and postoperatively.

Portacaval Shunts (37a)

RATIONALE

Formation of a venous by-pass to lower resistance to blood flow. Relief of portal hypertension reduces esophageal venous pressure. In our opinion, this is the procedure of choice where surgical decompression of the portal systems is desirable.

INDICATIONS

Hemorrhage from esophageal varices in patients where surgery is not contraindicated, there is no response to medical therapy and in whom hematologic studies reveal no gross clotting abnormality.

TECHNIC

There are two types of portacaval shunts which may be *employed* a direct anastomosis between a portal vein and the inferior vena cava, and splenectomy with anastomosis between the splenic vein and the left renal vein. Anastomosis of the portal vein and inferior vena cava may be done by a side-to-side or end-to-side procedure Implanting the distal end of the portal vein into the inferior vena cava *is considered preferable*

End-to-side splenorenal shunt with splenectomy has the advantage of removing the spleen when there is associated hypersplenism This has been the operation of choice with splenomegaly, and it is technically easier for there is an adequate vascular area for anastomosis

COMPLICATIONS

a Decrease in hepatic *reserve Some decrease in biochemical and physiologic reserve is always encountered However, in carefully* selected patients, this may not be significant

b Precipitation of acute hepatic insufficiency, jaundice, ascites, and or hepatic coma in patients with poor reserve

c Recurrent hemorrhage after the shunt procedure

d Occlusion of the shunt by secondary thrombosis Patency of a shunt may be evaluated by measuring the time required for ether or radioactive sodium to traverse the hemorrhoidal and portal systems to reach the systemic circulation

e Increased susceptibility to the meat intoxication syndrome

Ligation of Hepatic and Splenic Arteries (37b)

RATIONALE

Advocates of this procedure consider portal hypertension to be partly due to newly formed arteriovenous shunts with transmission of arterial pressure to the portal system It is believed that arterial ligation tends to reduce portal vein pressure and thereby decreases

the competition between venous and arterial constituents. This theoretically increases portal blood flow.

INDICATIONS

Hemorrhage from esophageal varices in a patient without jaundice, ascites, mental changes, or systemic hypertension, who is not responsive to medical management.

TECHNIC

The hepatic, splenic, and left gastric arteries are ligated close to the celiac axis.

COMPLICATIONS

a. Massive infarction of the liver. This hazard is reduced by use of antibiotics
b. Decrease in biochemical reserve secondary to ischemia.
c. Recurrent hemorrhage with lack of significant reduction of portal hypertension. A compilation of case reports shows a recurrence of hemorrhage in approximately 60% of patients.
d. Portal vein thrombosis.

HEMATOLOGIC DISTURBANCES

Anemia in patients with liver disease should be treated only after an attempt is made to determine its cause. Required studies may include peripheral smears, bone marrow, red blood cell survival studies, serum iron, etc. Whole-blood transfusions are required when there is a marked reduction in hemoglobin mass. They may be indicated also for anemia due to overt or subclinical hemolysis, or an abnormality in iron absorption. ACTH and adrenal steroids are valuable in treatment of the anemia of hypersplenism or acquired hemolytic disease. Splenectomy, performed as a part of the splenorenal shunt, is sometimes advisable in patients where a combination of hypersplenism and portal hypertension is responsible for symptoms. Although elective splenectomy without a shunting operation is not advisable, in our experience removal of the spleen alone has caused a disappearance of signs and symptoms of hypersplenism.

Iron deficiency anemia should be treated with oral iron. Rarely, parenteral iron or whole-blood transfusions are indicated in patients with a mucosal block which interferes with absorption of iron A low serum iron is present under these circumstances Extra iron should be avoided because the diseased liver has an increased affinity for iron although total body stores of this element are low

Macrocytic anemia is usually due to hemolysis but occasionally it is due to a deficiency of folic acid or vitamin B_{12} These substances are occasionally helpful in correcting anemia in liver disease Folic acid serves as a precursor of thiamine, and vitamin B_{12} serves as an essential metabolite in production of nucleic acid, both of which are required for manufacture of erythrocytes

Treatment of hemorrhagic tendencies depends upon the causative mechanism Fresh whole-blood transfusions are indicated as [illegible] be useful in decreasing [illegible] ion temporarily controls [illegible] amin K should be given for hypoprothrombinemia, although it is of little value in severe hepatic injury for the prothrombin deficiency results from decreased liver cell function A fibrinopenia rarely occurs but it can be corrected with purified fibrinogen now available commercially

SENSORIAL CHANGES AND HEPATIC COMA

Mental alterations in liver disease are due to both psychogenic and organic disturbances The most common mental change is delirium incident to alcoholism, drug therapy, or incipient hepatic coma Therapy consists of supportive measures and elimination of etiologic mechanisms wherever possible Reassurance and psychotherapy are of prime importance Hydrotherapy is desirable for control of physical hyperactivity Choice of sedatives is difficult because currently available agents are all detoxified by the liver Paraldehyde is the drug of choice in the absence of marked hepatic insufficiency because of its low capacity to induce delirium Specific measures include oxygen for anoxia, blood transfusions

for marked anemia, and vitamin therapy for vitamin deficiencies

At present therapy for hepatic coma is unsatisfactory and survival does not depend on current procedures (42) unless a specific abnormality such as hypoglycemia, anemia, low serum sodium, morphinism, or ammonium toxicity can be identified as the responsible mechanism It is important, therefore, to have a definite program so that nonhelpful therapeutic agents will not be employed at random The following therapeutic outline may be used as a guide·

1 *Laboratory procedures should include a blood sugar, hematocrit,* serum sodium, serum potassium, serum albumin, and a blood ammonium level An electroencephalogram may also be valuable
2 Give a minimum of 200 gm of a glucose-fructose mixture intravenously each day Correct marked abnormalities of circulating hemoglobin, protein or albumin by appropriate replacement.
3 Nalorphine should be given to counteract morphine Stimulants are given with mild barbiturate intoxication Artificial dialysis should be employed with severe barbiturate intoxication
4 Give 250 mg of tetracycline or oxytetracycline four times daily for its antibacterial effect
5 Give therapeutic quantities of vitamins B and C including 1000 mg. of ascorbic acid, 72 mg of vitamin K, 250 mg. of niacin, and 100 mg of thiamine for two to three days
6 Large doses of adrenal steroids or ACTH may be useful. This is particularly true in patients with acute viral hepatitis.
7. Give arginine or glutamic acid where ammonemia contributes to the clinical picture (This results in reduction of serum ammonium where ammonemia is due to receipt of ammonia salts, protein, or absorbed blood from the gastrointestinal tract, it is of little value with severe hepatic insufficiency where enzymes governing ammonia transformation are absent.)

Prophylaxis of hepatic coma includes: (a) *early recognition* and prompt treatment of hemorrhage and infections, (b) administration of intravenous albumin in critically ill patients following paracentesis, and (c) avoid morphine, short-acting barbiturates, and high protein dietary intakes in patients who have severe degrees of hepatic insufficiency or already have sensorial changes.

ASSOCIATED DISEASE STATES

Special attention should be given to the treatment of peptic ulcer, cholecystitis, coronary thrombosis, and other processes present concurrently with liver disease Peptic ulcer requires intensive therapy because complications such as hemorrhage and perforation are accompanied by a high morbidity and mortality Ten (70 per cent) of 14 patients with peptic ulcer and nutritional cirrhosis observed in our clinic presented therapeutic problems. six because of massive gastrointestinal hemorrhage, two because of intractable abdominal pain, and two because of perforation Antacids and antispasmodics should be used continuously in such cases to reduce acidity and prevent acid regurgitation into the esophagus

Treatment of cholelithiasis presents a major problem in patients with chronic liver disease. Recurrent episodes of cholecystitis or common duct obstruction as a result of calculi are accompanied by further hepatocellular damage Cholecystectomy is desirable to forestall irreversible liver injury Experience with 10 patients with nutritional cirrhosis subjected to surgical therapy for gallstones in the Jersey City Medical Center demonstrated an uneventful convalescence when there was adequate preoperative and postoperative care The patient with hepatic disease whose gallbladder does not visualize and who has symptoms of cholelithiasis also presents a therapeutic problem Nonvisualization may be due to liver dysfunction; whereupon surgical intervention is contraindicated On the other hand, patients with minor hepatic changes who have no visualization of the gallbladder should be suspected of having primary gallbladder disease and should receive surgery (43)

The coexistence of coronary thrombosis and hepatic disease presents a problem as to the selection of an appropriate analgesic, and the advisability of using anticoagulants to prevent thromboembolic phenomena. Morphine sulfate is well tolerated in the presence of compensated liver disease but may precipitate sensorial changes in patients with jaundice, ascites, or hepatic fetor

Other analgesics such as codeine or meperidine are preferable Anticoagulants may be given without ill effect, but because of the unpredictability of response to them, they should be omitted, if possible

Lowered host resistance in liver disease increases susceptibility to infectious diseases Infections are the third most common cause of death in nutritional cirrhosis, only hemorrhagic shock and hepatic coma being more common. Pneumonia is the most common type of infection Pulmonary tuberculosis and pyelonephritis also occur frequently Infections should be treated as if they were present without hepatic disease. Nevertheless, knowledge of a lowered resistance makes it desirable to rely more heavily on antibacterial therapy Choice of an antibiotic or chemotherapeutic agent should depend upon the identity of the offending organism Supportive measures are necessary and include correction of anemia and care for fluid and nutritional needs Microbial resistance to antibiotics is often present in liver disease because of interference with defense mechanisms such as phagocytosis and antibody formation

SURGERY

Surgical procedures in patients with hepatic disease are accompanied by a higher morbidity and mortality because of the vital role the liver plays in adjustment to stress Patients with liver injury have a decreased ability to metabolize adrenal steroids, detoxify anesthetic agents, and manufacture proteins and antibodies, all of which are essential for normal surgical convalescence It is, therefore, essential to provide as optimum conditions as possible in the preoperative period. This includes attention to fluid and electrolyte balance, circulating protein and hemoglobin, and adrenal reserve.

Choice of an anesthetic agent should be based on knowledge of the functional reserve of the liver and the pharmacology of the agent to be employed. The judgment of the anesthetist is important in selecting the drug to be used Vinyl ether, chloroform, ethyl chloride, and other substances which adversely affect the

normal liver should be avoided. Patients with mild to moderate hepatic dysfunction tolerate preanesthetic medications and have few ill effects from ether, cyclopropane, ethylene, barbiturate, or spinal anesthesia (44). Untoward effects are directly related to the degree of hepatic reserve, and appear to represent reaction to stress rather than toxicity of the anesthetic agent (45). In patients with moderate to severe liver injury, it is best not to use anesthetics such as barbiturates which are detoxified by the liver. All agents are risky with severe liver disease. However, regional block technics which do not affect sensorium or cause hepatic dysfunction are accompanied by few complications. Hypothermia may be a useful adjunct. It decreases the deleterious effect of hypotension and ischemia, and facilitates direct surgery on the liver by reducing the vascularity of this organ (46).

Surgical procedures on patients with liver disease should be followed by careful attention to hydration, electrolyte and nutritional balance, and general supportive measures. Intravenous supplements should be avoided and fluids limited to body needs during the immediate postoperative period. A high intake of carbohydrates is desirable. Decision as to ambulation must be individualized depending upon the severity of the liver disease, postoperative condition, and general physical status.

THERAPY BASED ON BIOCHEMICAL ALTERATIONS

Biochemical tests are used as a guide to therapy. No special attention need be directed to treatment of biochemical alterations in acute liver disease for such changes usually return to normal with general therapeutic measures. Sensitive tests such as the cephalin flocculation and bromsulfalein excretion are useful to determine when healing has occurred and treatment may be discontinued. In patients with chronic liver injury, treatment of decreased glycogen stores, a low serum albumin, or elevated serum bilirubin discovered as a result of these tests is often important.

A high oral intake of carbohydrates usually causes an improvement in results of the glycogen storage test. Transfusions in cases

of anemia, addition of vitamins for hypovitaminosis, lipotropic agents in fatty liver, insulin in diabetes, cardiotherapy in heart failure, and relief of biliary obstruction all help restore glycogen stores. Daily intravenous glucose and adrenal steroids are of value in patients refractory to these measures. Serial glycogen storage tests provide an objective measure of response to treatment

A low serum albumin is corrected by repeated infusions of human salt-poor albumin This often promotes a diuresis in patients with fluid retention when there is no response to restriction of sodium and water intake. It is desirable to determine repeatedly the total circulating albumin in order to gauge the effectiveness of salt-poor albumin therapy. Ascites and ankle edema frequently disappear when the concentration and total quantity of serum albumin increases

Persistent elevation of serum bilirubin requires special therapy. Corticotropin and adrenal steroids have a chloretic action which is of value where there is bilirubin retention due to primary cholangiolar injury (19) The prompt drop in serum bilirubin causes a decrease in pruritus and improvement in the well-being of the patient

THERAPY BASED ON HISTOLOGIC ALTERATIONS

The physician is interested in the prevention and control of fatty metamorphosis and necrosis of liver cells in acute hepatic injury An attempt should be made to alter the progression of fibrosis and nodular regeneration of liver cells Fatty liver is completely reversible by dietary means (47). Available therapeutic regimens which eliminate etiologic factors are good for control of necrotic reactions. In addition, general supportive measures, antibiotics, and adrenal steroids are helpful.

Hyaline necrosis associated with nutritional liver disease disappears on a high protein diet This type of necrosis is refractory to treatment when distortion of the architecture of the liver interferes with the blood supply. Liver cell necrosis secondary to bile stasis is reversible with relief of biliary obstruction Necro-

sis due to toxic and infective agents should be treated with specific antibiotics or chemotherapeutic agents (Table 16). These drugs are valuable for patients with limited degrees of liver cell necrosis. The central necrosis encountered in heart failure or shock is best treated by improving circulatory dynamics and correcting anoxemia.

In chronic liver injury, connective tissue alterations serve as a suitable gauge for therapeutic orientation if cognizance is made of other morphologic changes. Prognosis and response to therapy depend upon the cause (connective tissue proliferation or condensation of reticulum), degree (mild, moderate, or severe), and activity (active, or inactive) of hepatic fibrosis. Periodic histologic studies correlated with clinical and biochemical findings are desirable to evaluate response to therapy.

Our studies indicate that fibrosis of the liver is not spontaneously progressive and may be influenced by treatment (48). Current therapy is effective in the control of connective tissue proliferation in patients with mild to moderate active fibrosis. Mild fibrotic reactions due to condensation of reticular fibers are not evident after regrowth of liver cells. Severe fibrosis is usually refractory to treatment, although alterations in parenchymal cells improve with appropriate therapeutic measures.

Increased connective tissue activity and a transition from mild to moderate to severe hepatic fibrosis are noted when therapy is not available or successful. Although the fibrotic reaction serves as a reparative mechanism, necrosis and inflammation often continue or increase with connective tissue proliferation. The best therapeutic results are obtained in patients with mild or moderate active fibrosis.

A variety of substances including vitamin B_{12}, broad spectrum antibiotics and adrenal steroids, which have influenced connective tissue stroma in experimental animals, have been used as adjuncts to general therapy in patients with mild and moderate hepatic fibrosis. These investigations suggest that antibiotics and adrenal steroids in conjunction with rest, diet, and supportive measures may have helped suppress inflammatory reactions and fibroplasia in some patients. Additional study is required to determine the

role of these materials in long-term management. Attention to the status of the connective tissue stroma as well as parenchymal cells provides a new objective in treatment and further defines limitations of current therapeutic approaches (48).

EMPIRIC MEASURES

A large number of medicinal agents are given to patients with liver disease without an adequate pharmacologic basis. A composite approach permits the clinician to discard many of these materials and places proper emphasis on useful drugs and procedures. Available measures can be classified into those which are generally useful, those with a specific and limited utility, and those without demonstrated value. Rest, an adequate well balanced diet, and devices to control the etiologic mechanisms should be emphasized to all patients. Supplemental vitamins, lipotropes, salt-poor albumin, adrenal steroids, whole-blood transfusions, sodium restriction, diuretics and antibiotics are useful only if clinical, biochemical, and histologic findings indicate their need. Their indiscriminate use as supportive measures is not desirable. Current studies provide no basis for the general use of hematinics, liver extract, bile salts, insulin, and the host of other materials which are valuable in the individual patient with a specific defect.

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7

LIVER DISEASE DUE TO NUTRITIONAL DEFICIENCY AND METABOLIC DISTURBANCES

NUTRITIONAL deficiency is the most common cause of liver disease. Dietary abnormalities may be caused by the unavailability of proper food due to poverty or environment, and to fads imposed by habit, alcoholism, drug addiction, or disease. Poverty is responsible for consumption of food containing an inadequate amount of protein in many areas of the world. Alcoholism and drug addiction interfere with eating habits and produce similar degrees of nutritional deficiency. Therapeutic or selected diets are frequently inadequate and are responsible for malnutrition syndromes in diabetes mellitus, gallbladder disease, peptic ulcer, obesity, hyperthyroidism, malignancy, heart disease, and chronic infections (Fig 26)

Nutritional liver disease may be classified as follows: (a) mild, moderate, or severe fatty liver without fibrosis; (b) mild, moderate, or severe fibrosis with or without fat and/or hyaline necrosis.

PATHOGENESIS

An imbalance in normal dietary constituents leads to a fatty liver which undergoes fibroblastic transformation with continued

nutritional deficiency The extent of fat deposition is roughly proportional to the lack of lipotropic substances in the diet (1) These materials are necessary for oxidation or transportation of neutral fat (2) and must be supplied to prevent its accumulation Fatty acids accumulate in the liver as triglycerides when the

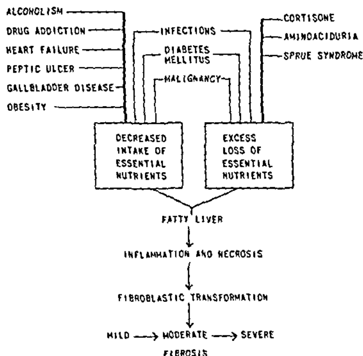


Fig 26 Evolution of nutritional liver disease.

lecithin (phosphatidyl-choline) synthesis does not occur at a normal rate (3) The presence of labile methyl groups is the important chemical characteristic which causes choline, methionine, betaine, and lipocaic to have lipotropic activity (Fig 27).

It has been possible to reconstruct the transition of fatty liver to nutritional cirrhosis in experimental animals (1), and from serial needle biopsy studies in man (1). In toxic processes, fat

may accumulate in the liver as a result of antilipotropic agents or depression of the enzyme systems which are necessary for normal fat metabolism Conglobation of intracellular fat produces large fat globules (Fig 28 top left) which displace liver cell nuclei and merge to form fatty cysts (Fig. 28 top right). The walls of the fatty cysts consist of reticulum and often contain several nuclei Continued distention of the fatty cysts causes their rupture. Collapse of the fatty cysts is accompanied by liver cell necrosis and

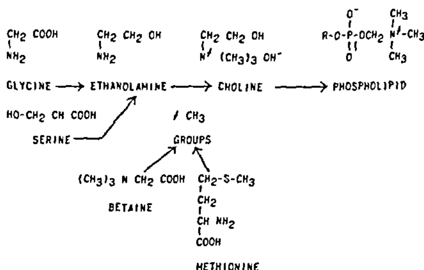
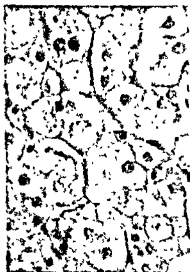


Fig. 27 Lipotropic substances, betaine and methionine furnish methyl groups for the formation of choline

an inflammatory reaction (Fig. 28 bottom left), and is followed by condensation of reticular stroma which form connective tissue septa (Fig. 28 bottom right) Spindle-shaped fibroblasts, inflammatory cells, and degenerated parenchymal cells can be detected in the newly formed connective tissue which dissects the lobule. Septum formation is demonstrable in the centrilobular as well as in the periportal areas in early nutritional cirrhosis. Fibrous connective tissue eventually separates the parenchyma from the vascular and biliary systems, and regenerated liver cells form nodules of two and three cell layers thick.









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Liver fibrosis in nutritional deficiency has also been attributed to proliferation of reticulum cells (5), fibroblastic transformation of mesenchymal cells (6), and serous exudation (7) Serous exudation is present with the inflammatory reaction but it has not been identified as the sole precursor of hepatic fibrosis. The following case history illustrates clinical, biochemical, and histologic alterations which occur with transition of a fatty liver to cirrhosis.

Case 5 Fibroblastic Transformation of Fatty Liver

Clinical Features L B, a 54-year-old housewife, was hospitalized in June 1948 with a history of emotional conflict and anxiety during the preceding several years arising from frustration in her home environment This led to ingestion of large quantities of beer and wine and maintenance of a poor dietary intake Physical examination revealed evidence of recent weight loss, anemia, an enlarged liver, and a smooth red tongue Treatment caused disappearance of all clinical abnormalities She was discharged to the outpatient department but did not return after several visits

The patient was rehospitalized in November 1952 because of weakness She had resumed ingestion of alcoholic beverages and maintained a diet consisting principally of carbohydrate foods Examination revealed a moderate macrocytic hemolytic anemia She responded to rest in bed, diet, vitamins, glucose infusions, and whole-blood transfusions given over a three month period She was discharged to the Liver Clinic but again failed to keep her appointments The patient was hospitalized with jaundice, ascites, and mental depression in April 1954 During the interval between hospitalization, she had continued to ingest alcoholic beverages and eat poorly

	1948 Before Therapy	*1948 After Therapy*	*1952*	*1954*
Hepatomegaly	4 cm	0	5 cm	6 cm
Splenomegaly	0	1 cm	0	0
Spider angiomas	0	0	1+	2+
Icterus	0	0	1	2+
Fluid retention	0	0	1	4+
Hepatic fetor	0	0	1+	4
Sensorial changes	0	0	0	4+
Bleeding esophageal varices	0	0	0	4+

	1948 Before Therapy	*1948 After Therapy*	*1952*	*1954*
Biochemical study				
Serum bilirubin (mg %)	0.3	0.4	2.2	27.2
Bromsulfalein (%)	6	0	32	..
Serum alkaline Phosphatase (B.U.)	2.3	2.6	6.5	4.5
Total serum cholesterol (mg %)	171	210	132	343
Cholesterol esters (mg %)	82	150	79	126
Serum albumin (Gm %)	3.1	4.2	2.5	2.8
Serum globulin (Gm %)	3.1	2.9	5.0	3.5
Cephalin flocculation	1+	0	2+	1+
Thymol turbidity (units)	1.0	1.0	5.0	5.0
Histologic study				
Fibrosis	0	0	2+	3+
Fat	3+	0	0	0
Regeneration	2+	1+	3+	3+
Bile stasis	0	0	1+	2+
Infiltration	1+	0	2+	2+
Necrosis	0	0	0	1+
Other	0	0	0	0
Pathologic diagnosis	Fatty liver	Normal liver	Moderate cirrhosis	Severe cirrhosis

Comment This case history represents the usual sequence of events which lead to nutritional cirrhosis. A combination of alcoholic beverages and an inadequate diet could be directly incriminated as responsible for fat accumulation and the subsequent fibrosis. Serial studies have demonstrated progression of fatty liver resulting from dietary indiscretion to advanced cirrhosis in 7 other patients followed over a six year period with serial clinical, biochemical and histologic studies. Poor dietary habits were attributable to alcoholism in 6 and to diabetes mellitus in 1 of this group

ETIOLOGIC MECHANISMS

Alcoholism

Alcoholism predisposes to fatty liver and cirrhosis since it decreases food intake, increases the need for lipotropic substances (8), and may interfere with oxidation of neutral fat (9) It is also possible that alcohol is a specific toxin or changes intermediary metabolism in some people Its interference with normal food intake appears to be the most important factor which causes liver disease Similar degrees of fatty metamorphosis are seen in nonalcoholic patients with poor dietary habits In a study of chronic alcoholics who eventually developed fatty liver there was no correlation between the amount, duration or type of alcoholic intake, and the onset of hepatic disease Needle biopsy of the liver in 66 alcoholic patients with delirium tremens in our clinic who had consumed similar quantities of alcoholic beverages revealed a normal liver structure in 19 (29 per cent), focal inflammation in 4 (6 per cent), fatty infiltration in 20 (30 per cent), and nutritional cirrhosis in 23 (35 per cent) (10)

Obesity

Nutritional liver disease is common in overweight patients because of their tendency to ingest a high carbohydrate, low-protein, high-fat, low-lipotropic diet Obese subjects store excessive amounts of fat due to an inability to utilize carbohydrate It has been suggested that decreased capacity to break down carbohydrate beyond the stage of pyruvic acid inhibits the utilization of fat and causes fat storage to gain ascendency over its mobilization and destruction (11) A poorly functioning liver may enhance defects in intermediary metabolism which predisposes to obesity Greatly overweight people always show laboratory and histologic evidence of liver disease (12) Hepatic damage is correlated with the degree and duration of obesity With marked obesity, bromsulfalein excretion carbohydrate tests, and serum lipid levels are abnormal Morphologic studies show fatty changes, cellular infiltration fibrosis and regenerative

phenomena. Biochemical and anatomic abnormalities disappear with reduction.

Diabetes Mellitus

The liver in diabetes differs from normal in that there is a decreased utilization of acetyl coenzyme A in the Krebs cycle, a decrease in fatty acid synthesis, and an underutilization as well as overproduction of glucose (13). These disturbances of intermediary metabolism are not accompanied by clinical signs unless there is an associated nutritional or other contributing factor (11).

A low protein intake coupled with these metabolic disturbances predisposes to nutritional liver disease and accounts for the increased incidence of fatty liver and cirrhosis in diabetes mellitus (15). Abnormal liver function tests were present in 40 per cent of 380 patients with diabetes mellitus studied in our clinic. This high incidence of liver dysfunction was related to the nutritional backgrounds of the patients studied Needle biopsy in 30 patients selected from this group revealed normal liver tissue in 14, fatty metamorphosis in 8, and nutritional cirrhosis in 8.

Age, sex, and duration of diabetes have no effect on the frequency of liver involvement Gross dietary and insulin insufficiency are often accompanied by liver dysfunction. Patients without complications have a lower incidence of liver function abnormalities than those with complications The incidence of hepatic dysfunction increases with coma, infections, and gangrene

Results of hepatic glucose uptake studies with hepatic vein catheterization prompted Sherlock to divide diabetic patients into *insulin sensitive and insulin insensitive groups* *Although there was* considerable overlap, young diabetics tended to be insulin sensitive and had normal hepatic histology, whereas adult diabetics were insulin insensitive and had fatty or fibrotic livers on biopsy In our experience histologic changes have been noted in *both* groups. Insulin resistance could not be correlated with anatomic changes

Studies of the etiologic interrelationship of diabetes mellitus and nutritional liver disease in the Jersey City Medical Center have revealed four groups. (a) diabetics in whom dietary restric-

tions and poor control caused fatty liver and cirrhosis, (b) patients in whom nutritional liver disease was accompanied by a diabetic syndrome and improvement of hepatic reserve caused disappearance of carbohydrate intolerance, (c) patients with latent diabetes where nutritional liver disease produced hyperglycemia and glycosuria, and (d) patients with concurrent diabetes and nutritional liver disease where no evident relation could be demonstrated. The following case history illustrates a patient with latent diabetes in whom transition of fatty liver to cirrhosis was accompanied by onset of clinical diabetes.

Case 6 Development of Clinical Diabetes with Progressive Hepatic Dysfunction

Clinical Features L. D., a 61-year-old bartender, was hospitalized in 1948 because of ankle edema. There was a familial history of diabetes mellitus. The patient had consumed four fifths of a quart of whiskey each day with good food intake except for periods of alcoholism. He had no symptoms of diabetes and a fasting blood sugar was on the borderline of normality. Following his discharge from the hospital, the patient returned to previous habits and noted onset of polyuria and polydipsia. Reevaluation in 1952 revealed progression of his hepatic disease, and symptomatic diabetes which required treatment with insulin. A glucose tolerance test showed a diabetic curve with no decrease in serum inorganic phosphorus.

Comment In some instances hepatic disease has caused a decrease in insulin requirements in patients with diabetes mellitus. Most patients have a simultaneous increase in severity of both diseases with inadequate therapy, and improvement of both conditions when adequate therapy is given. Numerous studies have been conducted on the relationship of poor nutrition to the degenerative vascular disease which is encountered in diabetes mellitus. Our observations demonstrate a high incidence of nutritional liver disease in patients with marked vascular complications. In one instance of poor dietary and insulin control, there was a progressive increase in insulin requirements and concomitant development of nutritional cirrhosis, diabetic retinopathy, nephropathy, and neuropathy.

Treatment of the diabetic patient with liver disease consists of appropriate dietotherapy, insulin, and measures to prevent infections

	1948	1952
Hepatomegaly	4 cm.	5 cm
Splenomegaly	0	1 cm
Spider angiomas	0	0
Icterus	0	0
Fluid retention	1+	0
Hepatic fetor	0	0
Bleeding esophageal varices	0	0
Biochemical study		
Serum bilirubin (mg %)	2.2	0.7
Bromsulfalein retention (%)	8	7.5
Total serum cholesterol (mg %)	291	362
Cholesterol esters (mg %)	198	239
Serum albumin (Gm %)	1.1	3.2
Serum globulin (Gm %)	3.4	3.6
Serum alkaline phosphatase (B U)	.	2.6
Cephalin flocculation	2+	2+
Thymol turbidity (units)		3.0
Blood sugar	125	229
Urine sugar	Neg	4+
Histologic study		
Fibrosis	0	3+
Fat	3+	1+
Regeneration	1+	3+
Bile stasis	0	0
Infiltration	2+	2+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	Fatty liver	Moderate nutritional cirrhosis

and complications of diabetes. Aryl sulfonylurea which suppresses glucagon, inhibit insulinase, or act through some other mechanism, reduce or eliminate abnormal glycosuria and hyperglycemia, and may be valuable in patients where hepatic factors contribute to carbohydrate disturbance. Preliminary studies by the author with Carbutamide have shown this preparation to be effective in control of hyperglycemia and glycosuria in patients with hepatogenic diabetes as well as in patients in whom hepatic disease precipitated clinical evidence of diabetes.

Endocrine Disturbances

Nutritional liver disease is seen in hyperthyroidism when increased energy requirements accentuate dietary inadequacies. Circulatory disturbances and toxic influences may be contributory but these are less important than the nutritional factors. It has been suggested by Moschcowitz that increased velocity of blood flow causes capillary sclerosis and eventually fibrosis in the subcapsular zone of the liver (16). We have observed fatty liver in three patients and nutritional cirrhosis in two patients with thyrotoxicosis. Needle biopsy of the liver showed no abnormalities in uncomplicated hyperthyroidism (17). During the present era of using radioactive iodine tracer studies to facilitate early diagnosis and treatment of thyrotoxicosis, hepatic lesions are rarely detected. Antithyroid therapy and an adequate diet usually control the hepatic lesion.

Cushing's syndrome due to adrenal hyperplasia, tumor, or exogenous administration of corticotropin or adrenal steroids is often accompanied by fatty liver. This condition is of interest since an intact liver is necessary for normal metabolism of these hormones. Fat accumulation may be related to disturbed carbohydrate metabolism. However, in most instances, it appears to be due to excess protein catabolism. Susceptibility to fatty metamorphosis depends on dietary habits, the status of the liver, and degree of hypercorticonism. A study in the Jersey City Medical Center showed fatty liver to be frequent in patients who ingest large amounts of carbohydrates or gain excessive weight while receiving adrenal steroids. This was noted in patients with normal liver morphology prior to therapy as well as in those with hepatitis, fat, or mild fibrosis. Appropriate dietary therapy is preventive. Testosterone also tends to interrupt the progression of fatty liver in these patients by its protein anabolic effect.

Nutritional liver injury may also occur in hypothyroidism, acromegaly, adrenogenital syndrome, testicular diseases, or ovarian diseases due to altered diet habits imposed by the endocrinologic disturbance.

	1948	1952
Hepatomegaly	4 cm	5 cm
Splenomegaly	0	1 cm
Spider angiomas	0	0
Icterus	0	0
Fluid retention	1+	0
Hepatic fetor	0	0
Bleeding esophageal varices	0	0
Biochemical study		
Serum bilirubin (mg %)	2.2	0.7
Bromsulfalein retention (%)	9	7.5
Total serum cholesterol (mg %)	294	362
Cholesterol esters (mg %)	198	239
Serum albumin (Gm %)	1.1	3.2
Serum globulin (Gm %)	3.4	3.6
Serum alkaline phosphatase (B U)	-	2.6
Cephalin flocculation	2+	2+
Thymol turbidity (units)	-	5.0
Blood sugar	125	229
Urine sugar	Neg	4+
Histologic study		
Fibrosis	0	3+
Fat	3+	1+
Regeneration	1+	3+
Bile stasis	0	0
Infiltration	2+	2+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	Fatty liver	Moderate nutritional cirrhosis

and complications of diabetes. Aryl sulfonylurea which suppresses glucagon, inhibit insulinase, or act through some other mechanism, reduce or eliminate abnormal glycosuria and hyperglycemia, and may be valuable in patients where hepatic factors contribute to carbohydrate disturbance Preliminary studies by the author with Carbutamide have shown this preparation to be effective in control of hyperglycemia and glycosuria in patients with hepatogenic diabetes as well as in patients in whom hepatic disease precipitated clinical evidence of diabetes

correlation between the amount of liver fat and nutritional habits Fatty metamorphosis in these circumstances may be due to a disturbance in enzymatic activity which is necessary for normal fat transport.

Infants and children appear to have an increased susceptibility to nutritional liver disease Excess liver fat is often found in infants dying of sepsis and gastrointestinal diseases It is an integral part of infantile pellagra and Kwashiorkor, where maintained dietary inadequacy eventually leads to cirrhosis (5) Focal necrosis is also

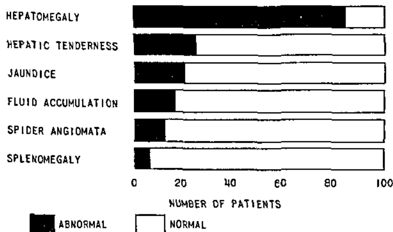


Fig 29 Clinical abnormalities associated with fatty liver

occasionally present in malnourished infants Serious exudation in the space of Disse has been noted as a precursor of hepatic fibrosis in Jamaican infants (7) Further study is necessary to determine if this lesion is of dietary origin or is due to a toxic process

FATTY LIVER

Clinical abnormalities are proportional to the degree of fat and disappear with its mobilization (Fig 29) No causal relationship can be established between fat accumulation and observed

Gastrointestinal Diseases

Approximately 30 per cent of patients with ulcerative colitis and 10–15 per cent of patients with peptic ulcer and gallbladder disease have nutritional liver disease. Fatty liver and varying degrees of hepatic fibrosis are observed in patients with colitis (18). These lesions are attributable to dietary imbalance imposed by therapy, anorexia, general debility, and toxemia. They must be differentiated by morphological study from viral hepatitis, which often occurs as a complication of whole-blood transfusions. Self-imposed or prescribed diets which are inadequate in essential nutrients appear to be the major cause for hepatic disease in peptic ulcer and cholelithiasis.

Other Diseases

Fatty liver may be seen in malignant neoplasms, heart failure, biliary obstruction, etc., and contributes to over-all morbidity of the primary disease. It is present in most patients with malignancy where there is anorexia or poor food absorption due to mechanical factors, general debility, or toxemia from the neoplastic process, radiotherapy or chemotherapy. Hepatic steatosis in patients with chronic circulatory congestion or biliary obstruction is related to ingestion of diets containing inadequate protein and lipotropic substances. This has been demonstrated by the fact that resumption of a normal food intake causes rapid disappearance of fat although morphologic evidence of congestion and bile stasis remain.

Fatty changes are prominent in patients with toxic or infective agents which cause hepatic injury. The damaged liver in toxopathic liver disease appears to have a greater proclivity for fat. Forced feeding and ingestion of large amounts of food because of diet prescription or therapeutic use of adrenal steroids sometimes causes a large fatty liver in viral hepatitis, rheumatic fever, general septicemia, toxemia of pregnancy, chronic low-grade carbon tetrachloride intoxication, phosphorus poisoning, and plumbism. Increase in liver lipids in these instances does not depend solely upon the nutritional state. However, there is often a

elevated serum bilirubin is due to a combination of direct and indirect reacting bilirubin. Hypercholesterolemia may reflect derangement of lipid metabolism and is present in patients with fatty liver who do not have impairment of bilirubin excretion or elevation of serum alkaline phosphatase. There is frequently an abnormality in the prothrombin time and glycogen storage tests.

Bed rest and a diet containing an adequate amount of protein and lipotropic substances causes the transformation of a severe fatty liver without fibrosis to a normal liver within a period of six to eight weeks. The general hospital diet with adequate protein, a high protein, low fat diet, and a high protein, high fat diet all produce similar results. Multivitamin preparations, choline and methionine, vitamin B_{12}, adrenal steroids, testosterone, and estrogens added to rest and diet do not shorten the time period required for removal of fat. With either regimen, some patients showed a slight amount of fat on biopsy at the end of 30 days. At the end of six to eight weeks, none of the patients showed significant liver fat (Table 14). The period of four to eight weeks required for removal of fat in patients with severe fatty metamorphosis suggests that time is as essential as the quantity of lipotropic substances (1).

Lipotropic agents are important for patients with anorexia or systemic diseases which interfere with food intake or assimilation. Patients who literally starve themselves have little or no liver fat. Choline, the production of which is influenced by various factors, appears to dictate the balance between accumulation and mobilization of fat. Exercise has no apparent effect on mobilization of fat and patients with fatty liver may be permitted to maintain moderate activity if they consume an adequate diet. A study in our clinic showed alcoholic subjects with a fatty liver maintained on a specially prepared high carbohydrate, high caloric, rice and fruit diet which contained little choline, had a disappearance of liver fat. This observation suggests that the human body may have stores of lipotropic substances which are available for use. Further investigation is required to determine the mechanism and significance of this finding.

The demonstration that fatty liver is a precursor of cirrhosis has led to periodic re-evaluation of patients with fatty liver (19).

signs and symptoms. Hepatomegaly is the commonest clinical sign and is attributed to accumulation of fat and edematous fluid. Hepatic tenderness and pain is the second most commonly encountered physical sign and may be sufficiently severe to simulate an acute surgical abdomen. Jaundice is occasionally present but is not proportional to the amount of liver fat. It is attributable to liver cell dysfunction, but in some instances, it may be due to mechanical compression of finer bile capillaries by extracellular fat. Splenomegaly which occurs in fatty liver is not accompanied by additional evidence of portal hypertension. The accumulation of ascites or edema is proportional to the amount of fat, however, malnourished patients with little fat have peripheral edema and ascites. Fatty liver may be associated with thrombocytopenia, blood clotting defects, blood sugar disturbances, azotemia, albuminuria, electrolyte depletion, decreased 17-ketosteroid excretion, and increased urinary estrogen.

Table 13 Biochemical Function Abnormalities in Patients with Fatty Liver

	%
Bromsulfalein excretion	50.6
Serum bilirubin	41.2
Serum alkaline phosphatase	20.0
Total serum cholesterol	54.1
Serum albumin	62.9
Serum globulin	80.7
Cephalin flocculation	9.4
Thymol turbidity	7.6
Cholesterol esters	14.5
Glycogen storage	92.9

There is no correlation between the amount of liver fat and the results of biochemical liver function tests (Table 13). Abnormal results of these tests are correlated with clinical evidence of malnutrition. The tests performed after elimination of fat show abnormalities until nutritional balance is re-established. The most frequent evidence of biochemical dysfunction is an alteration in plasma protein. There is no correlation between the amount of liver fat and the degree of protein changes. The bromsulfalein test is the most consistent index of severe fatty infiltration. Serum bilirubin usually ranges between 1.0 and 5.0 mg/100 cc. The

elevated serum bilirubin is due to a combination of direct and indirect reacting bilirubin. Hypercholesterolemia may reflect derangement of lipid metabolism and is present in patients with fatty liver who do not have impairment of bilirubin excretion or elevation of serum alkaline phosphatase. There is frequently an abnormality in the prothrombin time and glycogen storage tests

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Table 11 Effect of Various Therapeutic Regimens on Mobilization of Liver Fat

Regimen of rest plus	No. Patients	Fat mobilized in six weeks: None	0–10%	Over 10%
Rice and fruit diet (hypolipotropic)	3	2	1	0
General diet	3	2	1	0
High carbohydrate, high protein, low fat diet	4	3	1	0
High carbohydrate, high protein, high fat diet	2	1	1	0
Diet plus multivitamins	5	4	1	0
Diet plus multivitamins plus lipotropes	5	3	2	0
Diet plus cyanocobalamin	4	3	1	0
Diet plus lipoadrenal extract	3	2	1	0
Diet plus cortisone in small doses (25–50 mg. daily)	3	2	1	0
Diet plus therapeutic quantities of cortisone (100 mg. daily)	3	0	1	2
Diet plus estrogens (2.5 mg. Premarin daily)	2	1	1	0
Diet plus testosterone (25 mg. five times weekly)	2	1	1	0

Thirty per cent of such patients reaccumulated fat because of failure to maintain a proper diet. Fat has been removed and the development of cirrhosis forestalled by diet, rest, and supplemental measures. The following case history is illustrative.

CASE 7. RESPONSE OF FATTY LIVER TO 30-DAY PERIODS OF THERAPY

Clinical Features. P.C., a 37-year-old bartender, was admitted in 1951 with hematemesis and delirium tremens. He was a chronic alcoholic and consumed few protein-containing foods during long periods of continuous alcoholism. In 1953 and 1954, he was readmitted because of recurrent delirium tremens.

	1951		1953		1954	
	Before therapy	*After 1 mo of therapy*	*Before therapy*	*After 1 mo of therapy*	*Before therapy*	*After 1 mo of therapy*
Hepatomegaly	6 cm	0	8 cm	0	6 cm.	0
Hepatic tenderness	2+	0	0	0	0	0
Jaundice	0	0	0	0	0	0
Spider angiomas	1+	0	0	0	0	0
Fluid accumulation	0	0	0	0	0	0
Other	0	0	0	0	0	0
Treatment received	High protein, high carbohydrate diet		General diet		High carbohydrate, high protein diet plus cortisone	
Biochemical study						
Serum bilirubin (mg %)	0.0	0		0	1.0	0.1
Alkaline phosphatase (B U.)	1.9		1.8		2.8	2.7
Bromsulfalein (%)	15	0		0	34.5	4.0
Serum cholesterol (mg %)	246	134	226	253	316	276
Cholesterol esters (mg %)	334	213	134	126	191	103
Serum albumin (Gm %)	3.4	3.6	2.9	3.9	4.1	3.7
Serum globulin (Gm %)	3.1	4.6	3.0	2.3	2.0	2.6
Cephalin flocculation	2+	Neg	Neg	Neg	Neg	1+
Thymol turbidity	1.0	1.5	0.5	1.0	0.5	
Glycogen storage	7	54	24	50		53
Histologic study						
Fibrosis	0	0	0	0	0	0
Fat	4+	1+	3+	0	3+	2+
Regeneration	0	0	0	0	0	0
Bile stasis	0	0	0	0	0	0
Infiltration	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0
Other	0	0	0	0	0	0
Pathologic Diagnosis	Severe fatty liver	Mild fatty liver	Moderate fatty liver	Normal liver	Moderate fatty liver	Mild fatty liver

Comment. A hospital program designed to remove liver fat has been partly responsible for inhibiting fibrogenesis in this patient. Repeat studies in patients not given a period of intensive therapy to interrupt fat deposition have demonstrated development of fibrosis in 8 of 20 patients followed over a period of five years.

NUTRITIONAL CIRRHOSIS

Clinical features of fibrosis of the liver due to nutritional deficiency depend in part on the severity of the fibrosis and the degree

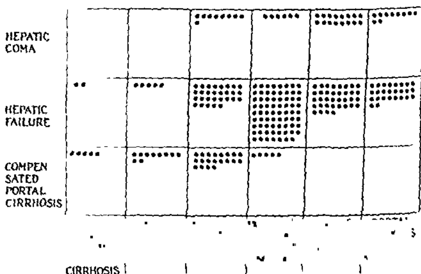


FIG 30 Clinical abnormalities associated with nutritional cirrhosis

of dissociation of the hepatic parenchyma from the biliary and vascular systems. Patients with mild nonactive fibrosis exhibit few signs and symptoms, stromal activity and moderate to marked fibrosis with loss of normal lobular architecture are accompanied by clinical evidence of hepatic insufficiency (Fig 30).

The subdivision of hepatic fibrosis into mild, moderate, and severe degrees on basis of needle biopsies obtained in vivo (see Chapter Four) has permitted a clearer understanding of the varia-

tion in clinical features of nutritional cirrhosis Attention has been centered on the degree of fibrosis in this classification, but of equal importance are the accompanying fatty, necrotic, and inflammatory changes in acute hepatic injury, and the nodular regeneration of liver cells, bile duct proliferation, and vascularization of the connective tissue in chronic liver disease

A study of gross postmortem specimens correlated with needle biopsies of the liver shows atrophic livers weighing from 700–1000 Gm in cases of severe nutritional cirrhosis The liver weight

Table 15 Physical Findings in 250 Patients with Nutritional cirrhosis

	Patients	
	No	%
Hepatomegaly	212	84 8
Jaundice	141	57 6
Ascites	114	45 6
Peripheral edema	105	40 2
Spider angiomas	101	40 0
Glossitis	77	38 0
Hepatic fetor	46	18 4
Hepatic coma	41	16 0
Splenomegaly	40	16 0
Abdominal collaterals	40	16 0
Pleural effusion	17	6 8
Peripheral neuritis	16	6 4
Testicular atrophy	8	3 2
Gynecomastia	7	2 8

ranges from 1000–3000 Gm. in moderate to severe cirrhosis without fat, depending upon the relative amount of connective tissue and liver cell regeneration With marked nodular regeneration of liver cells and moderate fibrosis, the weight ranged from 2000–3000 Gm , and from 2000–5000 Gm in cases in which fatty metamorphosis accompanied moderate cirrhosis Signs and symptoms are nonspecific in the absence of hepatic insufficiency. Hepatomegaly, jaundice, ascites, and spider angiomas usually reflect moderate to advanced hepatic fibrosis (Table 15). Marked varia-

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HEPATIC COMA

HEPATIC FAILURE

COMPEN SATED PORTAL CIRRHOSIS

FATTY LIVER WITH MILD PORTAL CIRRHOSIS | MILD PORTAL CIRRHOSIS | MODERATE PORTAL CIRRHOSIS WITH FAT | MODERATE PORTAL CIRRHOSIS NO FAT | SEVERE PORTAL CIRRHOSIS | PORTAL CIRRHOSIS WITH NECROSIS

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tions are noted in liver function tests. Serial evaluation shows a decrease in excretory and metabolic functional capacity with progression of fibrosis, and improvement when intensive therapy is given (Table 2).

Prolonged therapy is essential for nutritional cirrhosis The clinician should attempt to control fibroblastic activity and thereby prevent further liver cell injury. Intensive treatment is desirable as long as fibroblastic activity or inflammation is present in the connective tissue stroma, or the parenchymal cells are fatty or necrotic (20). A five-year follow-up study in patients receiving optimum treatment for mild and moderate fibrosis due to nutritional liver disease showed subsidence of inflammation in the connective tissue stroma, disappearance of fibroblasts, decrease in "ground substance," and shrinkage of collagen fibers This was accompanied by improvement of jaundice, fluid retention, and abnormal liver function tests (20). In severe fibrosis, the fibrotic process remained unchanged although fat and hyaline necrosis disappeared. Occasionally, parenchymal changes were first noted in patients with severe hepatic fibrosis during controlled in-patient therapy. This is attributed to difficulty in maintaining normal cell nutrition because of connective tissue barriers, nodular regeneration of liver cells, and formation of arteriovenous shunts. The following case history illustrates improvement of clinical, biochemical, and histologic abnormalities as a result of intensive therapy.

CASE 8 EFFECT OF THERAPY ON PATIENTS WITH MODERATE NUTRITIONAL CIRRHOSIS

Clinical Features H T, a 54-year-old laborer, was hospitalized in October 1949 because of jaundice and ascites. He had a history of

he maintained a good diet and consumed no alcoholic beverages. He was asymptomatic at the time of repeat study in June 1954.

Comment This case history illustrates the therapeutic response which can be obtained in patients with moderate nutritional cirrhosis Early

	1949	1951
Hepatomegaly	8 cm	6 cm
Splenomegaly	0	1 cm
Spider angiomas	2+	0
Icterus	1+	0
Fluid retention	4+	0
Hepatic fetor	1+	0
Sensorial changes	1+	0
Bleeding esophageal varices	0	0
Biochemical study		
Serum bilirubin (mg %)	2 2	0
Bromsulfalein retention (%)	7	0
Alkaline phosphatase (B U)	16 1	2 1
Total serum cholesterol (mg %)	176	353
Cholesterol esters (mg %)	59	191
Serum albumin (Gm %)	2 3	3 5
Serum globulin (Gm %)	4 8	2 3
Cephalin flocculation	4+	0
Thymol turbidity (units)	2 5	0
Histologic study		
Fibrosis	3+	2+
Fat	0	0
Regeneration	3+	2+
Bile stasis	0	0
Infiltration	2+	1+
Necrosis	1+	0
Other	0	0
Pathologic diagnosis	Moderate cirrhosis with fibroblastic activity in connective tissue stroma	Marked reduction of fibroblastic activity in connective tissue stroma

recognition and treatment of hepatic fibrosis is emphasized by the finding that neither connective tissue proliferation nor condensation of reticular fibers due to liver injury is spontaneously progressive. Both may be controlled by therapy.

Treatment of nutritional cirrhosis consists of rest, an adequate diet, and appropriate measures for complications such as jaundice, ascites, hematemesis, and mental changes. Disappearance of jaundice and hepatic fetor usually parallels improvement of other signs of hepatic failure. Ascites responds to therapy in most

patients on a regimen which includes sodium restriction and limitation of water intake to amounts lost, use of diuretics, correction of anemia, and repair of protein deficits Drastic sodium restriction prevents reformation of ascites in 80–90 per cent of patients Salt poor albumin appears to curtail accumulation of fluid in patients with a normal hemoglobin mass who do not respond to salt and water restriction Minor cerebral changes are reversible with treatment, hepatic coma is usually refractory. Bleeding from esophageal varices responds to whole-blood transfusions, balloon tamponage, and treatment of hemostatic defects in 60 per cent of

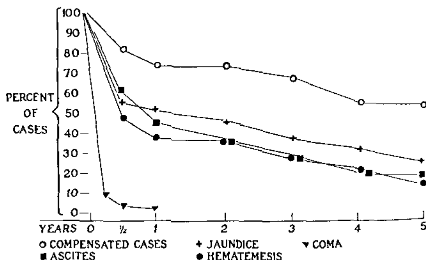


Fig 31. Survival after onset of major complications in 250 patients with nutritional cirrhosis

patients Shock and/or hepatic coma are responsible for death in patients who do not respond to this regimen.

Prognosis in patients with hepatic fibrosis due to nutritional deficiency depends upon the severity of the disease and ability to maintain a proper therapeutic regimen (20). Slightly more than one half of patients with hepatic fibrosis die during a 10-year period, approximately one third expire during the first year of treatment. Patients with mild fibrosis do not, as a rule, succumb to their disease. On the other hand, 25 per cent of patients with

moderate fibrosis and 50 per cent with severe fibrosis die within a period of one year after initial observation Jaundice, ascites, hematemesis, and mental changes are accompanied by rapid down hill courses Only 20 per cent of patients with nutritional cirrhosis and these clinical features treated in our clinic were alive at the end of five years (Fig. 31). Prognosis is also poor with marked abnormalities in biochemical liver function tests, blood clotting mechanisms, and electrolyte balance

Necrotic Liver

Liver cell necrosis is frequently present in patients with nutritional liver disease Postmortem studies demonstrate a much higher incidence of this morphologic finding than revealed by needle biopsies Simple necrosis is observed in most patients with fatty liver and usually disappears with appropriate therapy Hyaline necrosis is a more ominous sign. It is most often seen in patients with chronic liver disease after an alcoholic spree (21) Less commonly, it is seen on serial biopsy obtained during inpatient observation in the absence of alcoholism and acute dietary deficiencies

Alcoholism was present in 33 of 36 patients in whom biopsies showed hyaline necrosis in association with nutritional cirrhosis in our clinic Most patients had marked clinical and biochemical abnormalities, a few showed no clinical evidence of hepatic failure, and biochemical tests showed only minor changes Sensorial changes, gastrointestinal symptoms, and fluid retention were common complaints Signs of hepatic insufficiency were present in most patients and included hepatomegaly, hepatic tenderness, jaundice, and spider angiomas (Fig 32). Biochemical studies revealed an elevated bilirubin and abnormal protein pattern in each of the patients, bromsulfalein retention in 90 per cent, low cholesterol esters in 65 per cent, and positive cephalin flocculation in 60 per cent Other laboratory findings included azotemia, hyperglycemia, leukocytosis, and albuminuria A white blood cell count above 10,000 was present in two thirds of this group of patients

As a group, patients with hyaline necrosis respond poorly to

patients on a regimen which includes sodium restriction and limitation of water intake to amounts lost, use of diuretics, correction of anemia, and repair of protein deficits. Drastic sodium restriction prevents reformation of ascites in 80–90 per cent of patients. Salt poor albumin appears to curtail accumulation of fluid in patients with a normal hemoglobin mass who do not respond to salt and water restriction. Minor cerebral changes are reversible with treatment, hepatic coma is usually refractory. Bleeding from esophageal varices responds to whole-blood transfusions, balloon tamponage, and treatment of hemostatic defects in 60 per cent of

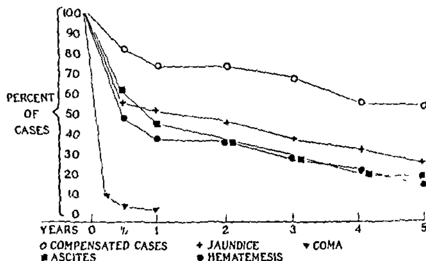


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	Initial study 1948	*Second study 1952*	*Third study 1953*	*Study after 2 mos of treatment*
Hepatomegaly	3+	3+	3+	3+
Splenomegaly	0	0	0	0
Spider angiomas	1+	1+	1+	1+
Icterus	1+	0	3+	1+
Fluid retention	1+	2+	2+	1+
Hepatic fetor	0	0	0	0
Sensorial changes	0	0	0	0
Bleeding esophageal varices	0	0	0	0
Biochemical study				
Serum bilirubin (mg %)	1 8	0 5	10 3	1 8
Bromsulfalein retention (%)	0	0		22
Serum alkaline phosphatase (B U)		8 5	10 7	7 5
Total serum cholesterol (mg %)	232	143	206	246
Cholesterol esters (mg %)	77	79	77	138
Serum albumin (Gm %)	2 4	3 4	1 7	3 3
Serum globulin (Gm %)	4 4	3 4	5 1	2 3
Cephalin flocculation	Neg	3+	3+	2+
Thymol turbidity (units)		2 0	10 0	1 5
Histologic study				
Fibrosis	0	3+	3+	3+
Fat	4+	1+	2+	0
Regeneration	0	3+	2+	1+
Bile stasis	0	0	0	0
Inflammation	0	2+	3+	1+
Necrosis	0	0	1+	0
Other	0	0	0	0
Pathologic diagnosis	Fatty liver	Moderate cirrhosis	Moderate cirrhosis with hyaline necrosis	Moderate cirrhosis

therapy. Most patients with this lesion have severe fibrosis with almost complete dissociation of the hepatic parenchyma from its blood supply In several instances, serial needle biopsy has demonstrated a reversal of hyaline necrosis where architectural changes were not marked *The following case history illustrates the* response to therapy of hyaline necrosis in a patient with moderate hepatic fibrosis

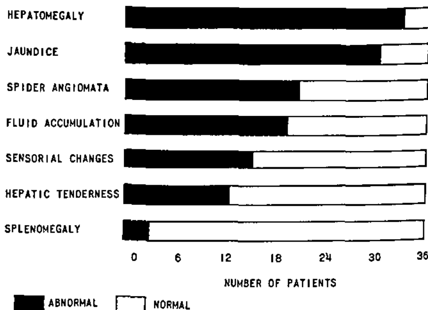


FIG 32 Clinical abnormalities associated with hyaline necrosis in nutritional cirrhosis

CASE 9. RESPONCE TO TREATMENT IN PATIENTS WITH HYALINE NECROSIS AND NUTRITIONAL CIRRHOSIS

Clinical Features J B, a 65-year-old male, chronic alcoholic patient with prolonged dietary inadequacy, was hospitalized for a subtotal gastric resection because of pyloric obstruction secondary to peptic ulcer A biopsy showed evidence of fatty liver An attempt was made to rehabilitate him However, he returned to alcoholism and poor dietary habits upon discharge from hospital care He was readmitted in 1952 and 1953

conditions which may be accompanied by excessive iron deposition. In the Jersey City Medical Center, for study purposes, patients with excessive hepatic iron have been divided into three groups (a) those with an intracellular metabolic abnormality of the liver permitting accumulation of extra liver iron, (b) those with increased absorption of iron from the gastrointestinal tract, and (c) those with lack of utilization of parenteral iron Each of these groups includes patients with and without fibrosis and with and without clinical stigmas of hepatic disease This formulation is useful for clinical research

Intracellular Disturbances

Patients with acute liver damage due to viral hepatitis, heart failure, and malnutrition, as well as those with fibrosis occurring with these etiologic mechanisms, sometimes have a visible increase in iron pigment It has been postulated that intracellular metabolic changes cause iron to accumulate in relation to mitochondria (6) Clinical recognition of increased liver iron due to this mechanism is difficult unless previous biopsies have been performed The iron is distributed in both parenchymal and reticuloendothelial cells Serum iron levels and radio-iron absorption are usually normal although nutritional changes in the intestinal tract or pancreas may develop to alter expected findings Treatment consists of measures for the underlying hepatic disease

Hemochromatosis

Increased iron absorption is characteristic of idiopathic familial hemochromatosis, the cytosiderosis seen in South Africans, and others with malnutrition (6). Hepatic content of iron may increase to 15–20 Gm. (Fig 33). Diagnosis is based on radio-iron uptake studies Unfortunately, variation in iron absorption with the nutritional state and other factors decreases the specificity of this test In a positive test, 60–80 per cent of ingested radio-iron may be absorbed (22c)

A diagnosis of hemochromatosis should be suspected in the presence of liver fibrosis, diabetes, and excess liver iron This disease occurs principally in men, and is most often seen in the age

METABOLIC DISTURBANCES

Inborn or acquired errors of metabolism involving carbohydrate, protein, fat, and iron are commonly responsible for hepatic disease. In most instances, the causative mechanism is congenital and often familial These diseases have been observed in both pediatric and adult medicine but their natural history has not been completely worked out.

Iron Storage Disturbances

Excess liver iron is a common metabolic disturbance which is observed in chronic malnutrition; as a familial disorder, following numerous blood transfusions, or infusion of saccharated iron; and as a complication of chronic hemolytic disease, chronic infection, or ingestion of large quantities of dietary iron. The iron content of histologically normal livers ranges from 0 01–0.05 per cent of dry weight of tissue (6). Approximately 12.5 per cent of total body iron (4–5 Gm.) is stored in the liver. The ordinary diet contains about 15 mg of iron, and of this, only 10 per cent or 1 5 mg is absorbed daily through the duodenal mucosa. Under the in-influence of gastric acidity, highly insoluble ferric hydroxide is reduced to more soluble ferrous hydroxide. Ingested iron enters the mucosal cells and combines with apoferritin, an iron-free protein to form ferritin, the storage form of iron. Ferritin acts as a blocking agent to prevent excess iron absorption. Ferric hydroxide is reduced and enters the blood stream where it is combined with siderophilin to form a complex in which form it is transported to the tissues Normally, siderophilin is only one-third saturated with iron, the normal serum level being about 100 µg./100 ml The total iron binding capacity of protein is about 300 µg. (22)

Ferritin is a brown compound which does not have any histochemical specificity with available iron stains. Polymerization of ferritin presumably leads to larger granules of hemosiderin which is identified by the Prussian blue reaction.

Numerous classifications have been offered to group the many

conditions which may be accompanied by excessive iron deposition In the Jersey City Medical Center, for study purposes, patients with excessive hepatic iron have been divided into three groups. (a) those with an intracellular metabolic abnormality of the liver permitting accumulation of extra liver iron, (b) those with increased absorption of iron from the gastrointestinal tract, and (c) those with lack of utilization of parenteral iron Each of these groups includes patients with and without fibrosis and with and without clinical stigmas of hepatic disease This formulation is useful for clinical research

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A diagnosis of hemochromatosis should be suspected in the presence of liver fibrosis diabetes, and excess liver iron. This disease occurs principally in men, and is most often seen in the age

group 45–55 There is an increased amount of iron in the pancreas, skin, heart, spleen, thyroid, parathyroid, anterior pituitary and salivary glands Lesser amounts occur in the gastrointestinal and genito-urinary tracts. The pancreas is hardened and fibrotic in 90 per cent of patients, iron is deposited in acinar epithelium fibrous tissue and islands of Langerhans. Lipofuscin is seen in the blood vessel walls and connective tissues. Skin pigmentation occurs due to increased melanin in the deep layers of the epidermis, and hemosiderin in the corium. Hemosiderosis of the myocardium occurs in many cases and may predispose to cardiac disability Mild to severe insulin-resistant diabetes is encountered. This may be due to pancreatic damage, hepatic insufficiency, or a combination of these factors. Hypogonadism resulting from liver dysfunction or iron deposition in endocrine organs is often present. Occasionally, hypotension occurs due to adrenal, hepatic, or myocardial dysfunction secondary to iron deposition. Biochemical liver function studies reveal no specific disturbance with iron accumulation but reflect basic functional capacity which may be altered by many morphologic changes A roentgenogram of the abdomen may reveal stippling in the normal hepatic area due to radio-opacity of the accumulated iron

There is no correlation between hepatic iron and connective tissue changes Advanced hemosiderosis may be associated with little alteration of connective tissue, and mild iron accumulation may be associated with marked hepatic fibrosis Liver biopsies show iron predominantly in the parenchymal cells. However, Kupffer cells may contain large quantities of iron. Hemofuscin, an iron-free lipochrome, is usually present in large quantities The serum iron is usually elevated and the iron tolerance test where 10 mg. of elemental iron is given intravenously shows a high DEC/INC ratio in hemochromatosis (above 20). In this test, a serum iron is measured in the fasting state, after five minutes, and after two hours. The five minute level gives the total iron binding capacity, the difference between the five minute and fasting level is called the increase, and from the five minute to the two hour level is called the decrease. The DEC/INC ratio represents the relative uptake of iron by the tissues (22d).

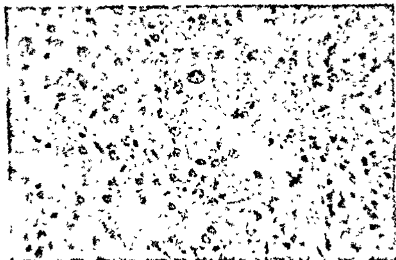


Fig 33 Hemosiderosis of the liver (hemosiderin represented in golden brown)



Fig 34 Primary amyloid of the liver (amyloid represented in blue)

Treatment depends on the amount of iron present and the severity of associated liver disease Use of interval phlebotomy or chelating agents to reduce visible hepatic iron is accompanied by improvement in clinical and biochemical abnormalities (23c) Iron absorption is controlled by a low iron, high phosphorus diet This program should be coupled with general therapy for liver disease which includes a high protein, moderate carbohydrate diet, and insulin in sufficient quantities to control hyperglycemia and glycosuria Death may result from diabetic acidosis, massive gastrointestinal hemorrhage, hepatic coma, superimposed infections, or primary liver cell cancer (24) Prognosis is fairly good with the newer technics for preventing and controlling diabetic ketosis and complications of hepatic disease

Lack of Utilization of Exogenous Iron

Excessive destruction of erythrocytes in hemolytic anemias, repeated blood transfusions, and intravenous iron therapy cause an accumulation of iron pigment in the Kupffer cells (25) Liver cell iron is increased if the responsible mechanism continues This type of process is usually recognized by history Initially, liver biopsies show iron predominantly in the Kupffer cells, but with large iron overloads, hemosiderin also accumulates in liver cells Serum iron levels, tolerance to intravenous iron and oral radio-iron absorption tests show variable results because of the influence of the underlying pathologic condition Thus in anemia due to bone marrow depression there may be increased iron absorption, hyperferremia, and abnormal iron tolerance Iron deposition in other organs is less widespread than in hemochromatosis There may be varying degrees of hepatic fibrosis The severity of fibrosis, liver size or spleen size is of no value in deciding the mechanism of abnormal iron deposition unless correlated with other data We have seen several patients with advanced hepatic fibrosis who have developed iron overload as a result of hemolysis or transfusions Clinical stigmas as diabetes, hypogonadism, and other signs or symptoms which can be related to liver dysfunction are likewise nonspecific findings and may have no bearing on the etiologic process

Treatment of excess iron deposition following transfusions appears to be important particularly in individuals who require *prolonged use of transfusions* Chelating agents such as ethylenediamine-tetraacetic acid, will permit removal of excess iron (26) while allowing the patient to profit from a periodic increase in circulating hemoglobin mass (23b).

Amino Aciduria

Diseases characterized by amino acidura are often associated with hepatic damage. Hepatolenticular degeneration (Wilson's disease) and the Fanconi syndrome are the common metabolic diseases which fall into this category. There are a number of variants of these conditions which are *not accompanied* by liver injury.

Wilson's Disease

Hepatolenticular degeneration is a familial disorder which is characterized by the triad of basal ganglia degeneration, pigmentation of Descemet's membrane of the limbus of the cornea (Kayser–Fleischer ring); and hepatic fibrosis. Liver disease as well as central nervous system changes have been attributed to: (a) nutritional deficiency secondary to persistent amino acidura; (b) disturbances in copper metabolism; and (c) an unknown toxin which causes the encountered morphologic and biochemical alterations.

Most students of this disease believe an error in copper and/or amino acid metabolism is the basic mechanism responsible. It has been suggested that liver damage results from the chronic loss of amino acids, and copper accumulates in the tissues due to chelation between the copper and peptide residues (27). A second school feels the primary abnormality is increased absorption and tissue storage of copper, with secondary injury of the kidney tubular epithelium causing amino acidura (28). Recently, emphasis has been put on the demonstrated inability of patients to synthesize coeruloplasmin which leads to increased absorption of copper from the gastrointestinal tract and excess deposition of copper in the brain, liver, and kidney (29).

The brain lesions consist of degeneration in the putamen, globus pallidus, and caudate nuclei, varying from necrobiosis to atrophy and cyst formation. Nerve cells are replaced by glial cells in many instances. Patients may have fatty liver or varying degrees of hepatic fibrosis. The fibrosis may be diffuse or of the postnecrotic scarring variety.

Clinically a diagnosis is suspected by the presence of signs of basal ganglion disease in a patient with evidence of hepatic disease. The disorder occurs in both sexes, beginning during childhood or young adulthood. Paralysis agitans is simulated by tremulousness, choreic and athetoid movements, rigidity of the extremities and facial muscles, dysphagia and dysarthria, and psychic changes. The finding of a Kayser–Fleischer ring, which is present in chronic phases of the disease, facilitates a diagnosis. Slit lamp study may be required for its detection.

Clinical stigmas vary from no abnormalities to evidence of hepatic failure including icterus, ascites, spider angiomas, hepatic fetor, and bleeding esophageal varices. Biochemical liver function studies establish the presence of hepatic dysfunction and provide an objective baseline to evaluate therapeutic response. Results of liver function tests depend upon the histologic severity of the disease process. The presence of amino aciduria, an elevated urinary excretion of copper, and a low plasma level of copper is suggestive of the disease from a laboratory point of view.

Therapy is not specific. An attempt should be made to decrease body copper by reducing its absorption and by increasing its excretion. A high protein diet increases amino aciduria and thereby accelerates copper loss. Potassium sulfide decreases copper absorption and should be given in doses of 20 mg three times daily. British anti-lewisite (BAL) causes copper excretion when it is taken in 5–10-day courses consisting of 25 mg/Kg. twice daily (29). The improvement in neurologic findings demonstrable with use of chelating agents suggests that the excessive copper in the brain is loosely bound and the tissue affinity is easily overcome. However, copper depletion used alone does not improve hepatic function. Supportive measures are necessary to repair

and prevent further liver damage and to control neurologic symptoms

Fanconi's Syndrome

Fanconi's syndrome is principally a childhood disease which is characterized by hypophosphatemic rickets, renal glycosuria, and amino aciduria. Hepatic lesions are less frequent in this syndrome than in Wilson's disease. Anatomic studies show characteristic changes in the kidney tubules (30). Renal tubular dysfunction *leads to a deficient reabsorption* of phosphates, glucose, and amino acids. An associated acidosis due to retention of hydrogen ions lowers the renal threshold for phosphorous. Phosphaturia causes an increased loss of calcium and leads to renal rickets. Patients who survive for long periods have hepatic injury which presumably results from persistent glycosuria and amino aciduria (31). The liver may be normal, fatty, or fibrotic depending upon the duration and severity of these metabolic defects.

The diagnosis should be suspected in patients who present evidence of rickets with or without signs and symptoms of hepatic disease. *The diagnosis is confirmed by demonstrating renal glycosuria* and amino aciduria. The serum amino acid level is normal. Treatment is largely supportive. Attempts to correlate nutritional deficiencies and the low serum phosphorus have not been successful.

Glycogen Storage Disease

Glycogen storage disease may involve primarily the liver or heart, or both of these organs. Gargoylism represents a related metabolic disturbance with a genetically induced defect in the metabolism of structural polysaccharides. The hepatic type of glycogen storage disease is characterized by an enlarged liver, retarded development, and hypoglycemia. *It is first evident in infancy or early childhood* and is due to an error in phosphorylating glucose. There is a deficiency of glucose 6-phosphatase which is necessary for glycogenolysis. Large amounts of glycogen accumulate in the liver parenchyma and the blood sugar is reduced to hypoglycemic levels. The liver and kidneys are enlarged

due to accumulation of intracellular glycogen The liver cells appear to be laden with fat, but clear spaces are always intracellular Best's carmine stain permits histochemical identification of glycogen.

Symptoms are due to hypoglycemia and include tachycardia, sweating, sensorial changes, or convulsions An enlarged liver accompanied by a low blood sugar which is not altered by epinephrine or glucagon is a suggestive sign The diagnosis is confirmed by demonstrating excess glycogen in a liver biopsy specimen

Therapy is unsatisfactory, although some patients survive to the second and third decade with this disease In acute phases, heroic measures are necessary A high protein, high carbohydrate, high vitamin diet, and corticotropin or adrenal steroids are indicated Feedings should be frequent to prevent hypoglycemia which leads to brain damage or may be fatal if not controlled

Galactosemia

Galactosemia is an inborn error of galactose metabolism characterized by an inability to convert galactose to glucose It occurs in infants and is accompanied by marked weight loss, hepatomegaly, varying degrees of hepatic failure, amino aciduria, cataracts, and mental deficiency Normally, ingested galactose is phosphorylated by galactokinase and ATP, galactose-1-phosphate is then converted to glucose-1-phosphate by activity of P-Gal transferase and Galacto-waldenase Biochemical studies suggest galactosemia is due to absence of the enzyme P-Gal transferase (32) Galactose accumulates in the blood and causes liver enlargement, amino aciduria, and early death if the condition is not recognized and properly treated Survivors may have persistent liver damage, mental retardation and cataracts Hepatic lesions consist of fatty or fibrotic changes in addition to excess glycogen in parenchymal cells

The diagnosis of galactosemia should be suspected in any infant with gastrointestinal symptoms associated with liver enlargement Spectrophotometric studies are diagnostic Erythrocytes from galactosemic subjects incubated with galactose demonstrate

an accumulation of galactose-phosphate. Galactose tolerance tests show marked impairment, much more than would be expected from clinical evidence of hepatic disease. Galactosuria may be detected by paper chromatography or chemical methods.

Treatment with a lactose and galactose free diet often dramatically relieves the symptoms of galactosemia. Casein digests supplemented with sucrose, vitamins, minerals, and water provides ample nutrition in the acute phase when the diet should be absolutely free of galactose containing substances. One patient followed with this defect for a period of five years in our clinic has had no residual defects following control of the acute process

Lipoidosis

The lipoidoses often simulate primary hepatic disease because of liver involvement. *Xanthomatosis, the most common malady* of this type, may be secondary to chronic biliary obstruction Xanthomatous diseases may be accompanied by hypercholesterolemia or normocholesterolemia (32). Increased endogenous production of cholesterol is associated with xanthelasma and atherosclerosis. There is also an elevated serum cholesterol and phospholipids, and an increase β_1 globulin fraction in the serum.

Essential hyperlipemia (elevation of neutral fats) is usually associated with an enlarged liver and spleen. The characteristic clinical features of the familial variety of hyperlipemia (essential hyperlipemia) consist of hepatosplenomegaly, eruptive xanthomas, and lipemic retinalis. The xanthomas appear as small yellow papules noted over the entire surface of the body. Recurrent severe abdominal pain associated with an elevation of the serum amylase has been recorded, and was noted in a patient observed by the author Needle biopsy of the liver in this patient showed no significant abnormality. The interrelationship of disturbed lipid metabolism and pancreatic involvement is not clear, but it has been suggested that the elevated serum lipid stimulates the pancreas and is responsible for encountered symptoms (33) The diagnosis of hyperlipemia is based on the presence of a milky serum in the absence of diabetes and pancreatic disease Lipid studies reveal an elevated total level sometimes reaching 5000

mg /100 cc. and consisting of increased neutral fat, phospholipids, and free cholesterol Treatment consists of prolonged use of low fat diets, sitosterol, or estrogens

Marked hepatic abnormalities occur in patients with Letterer-Siwe's disease, Gaucher's disease, and Neimann–Pick's disease, whereas hepatic changes have been notably absent in patients with eosinophilic xanthomatous granuloma Hepatic alterations are due to accumulation of the abnormal lipids in the liver which cause compression atrophy. Fatty or fibrotic changes may occur secondary to nutritional deficiency Diagnosis of these disorders depends upon identification of the abnormal lipid, the presence of a normal serum cholesterol, and clinical features characteristic of the disease (34) Treatment is supportive except for eosinophilic granuloma of a localized variety which is amenable to surgical extirpation

Two infants with Letterer–Siwe's disease observed in the Jersey City Medical Center had marked hepatocellular dysfunction related to compression of hepatic cells by lipid infiltrates Gaucher's disease is notably associated with an enlarged liver and spleen, hemorrhagic tendencies, lymphadenopathy, and patchy skin pigmentation Hepatic involvement may simulate decompensated hepatic cirrhosis and is due to accumulation of cerebrosides in histiocytes of the reticuloendothelial system The diagnosis is established by finding Gaucher cells in the bone marrow or liver Niemann–Pick's disease, which produces a similar clinical picture, is due to an accumulation of sphingomyelin Foam cells cause enlargement of the liver and distort its lobular pattern in advanced stages

Amyloidosis

Amyloidosis is an acquired metabolic disturbance which often involves the liver. It has been classified into a primary and secondary variety on the basis of etiology, organ location, and affinity for special stains (35) In primary amyloidosis, there is no associated etiologic mechanism which is evident, the tongue, skin, myocardium, and gastrointestinal tract, and less frequently the liver, kidney, and spleen, are involved in the process, and there is

no affinity for Congo red or iodine. Secondary amyloidosis occurs during the course of chronic infections and degenerative diseases, involves the liver, kidneys, spleen, and adrenals, and is readily stained with Congo red and iodine This classification is unsatisfactory for patients with so-called primary amyloidosis often have hepatic involvement.

In patients with hepatic amyloid, the amyloid is deposited between the endothelial cells of the sinusoids and may cause compression atrophy of the parenchymal cells (Fig. 34). Clinical features depend upon the presence of other diseases and the organs involved Signs and symptoms of osteomyelitis, tuberculosis, rheumatoid arthritis, and multiple myeloma which are frequently associated with amyloidosis may dominate the clinical picture Hepatomegaly, splenomegaly, jaundice, and fluid accumulation are often present and simulate nutritional cirrhosis Biochemical liver function tests are usually only slightly deranged, although they may be markedly abnormal.

Biopsy of the liver, gums, or kidney provides the best method of demonstrating amyloid The Congo red test, which is positive with marked hepatic involvement, is helpful. Disappearance of 90 per cent or more of the dye from the serum is indicative of amyloid Search for albuminuria due to renal involvement and electrocardiographic alterations due to myocardial changes is desirable in establishing the extent of the process

Treatment is usually unsatisfactory where therapy must be primarily directed to the amyloid Control of infection or multiple myeloma appears to forestall progression of the process, and in some instances causes a regression of amyloid (36).

Porphyria Hepatica

Recent studies by Watson and his associates (37) show that porphyria *most commonly results from an inborn error* involving the regulation of porphyrin metabolism in the liver. Hepatic porphyria must be differentiated from porphyria erythropoietica, a congenital form of the disease first noted in infancy and characterized by red urine, skin photosensitivity, reddish-brown discoloration of the teeth, and oftentimes splenomegaly and a hemo-

lytic anemia Erythroblasts produce increased amounts of uroporphyrin and coproporphyrin, and bone marrow study is, therefore, diagnostic

Porphyria hepatica has been classified into an intermittent acute, cutanea tarda, mixed and latent types Icterus is occasionally present and most patients have abnormal bromsulfalein excretion Needle biopsy of the liver shows increased amounts of a precursor of porphyrin in the intermittent acute type and elevated levels of preformed porphyrin in the cutanea tarda group Porphyria hepatica must be distinguished from simple porphyrinuria noted in chronic liver disease (see Chapter Three) Occasionally patients with cirrhosis of the liver will have urinary porphobilinogen and increased urinary uroporphyrin probably due to latent porphyria

A pink to red fluorescence of urine (normal, acidified, or heated) under ultraviolet light is highly suggestive of porphyria The chloroform insoluble Ehrlich aldehyde test for porphobilinogen (Watson-Schwartz) is a reliable test for porphyria and along with increased levels of urinary uroporphyrin appears to be specific for this disease Nevertheless, it is desirable to confirm the presence of porphyrin by demonstrating an absorption band with a hand spectroscope, maximum at 560–565 mμ Further identification is possible by determining melting points of the methyl esters or by paper chromatography

Intermittent acute porphyria is characterized by recurrent severe, colicky abdominal pain, and neurologic signs and symptoms The latent form of the disease may become symptomatic following administration of barbiturates, alcohol, or other chemicals Abdominal pain has been attributed to smooth muscle spasm and distention Neurologic and psychiatric disturbances include a variety of syndromes involving the cortex, hypothalamus, medulla, spinal cord, and peripheral nerves Occasionally hypertension is prominent, rarely, symptoms and signs of adrenal insufficiency are the presenting clinical features

Porphyria cutanea tarda is less common and is characterized by skin sensitivity leading to vesicles and bullae in areas exposed to light heat, or trauma Liver disease may be present as demon-

strated by clinical, biochemical and histologic studies. The cutaneous type may be combined with intermittent acute porphyria and the symptom complex include abdominal and/or nervous system manifestations.

Treatment consists of avoiding drugs known to precipitate acute attacks, and symptomatic measures. Parenteral feeding and tracheotomy are often necessary with bulbar paralysis ACTH or corticosteroids may be valuable if given for a period of five to seven days, although in some instances there is no improvement with this therapy. Massive doses of prednisone had little effect on one patient with hepatic porphyria observed in association with Dr. George Calvy and associates at St. Albans Naval Hospital. Folic acid, riboflavin, and vitamin B_{12} may be helpful. Tetraethyl ammonium followed by splanchnicectomy produced an amelioration of symptoms in one patient with severe abdominal pain (37). Chlorpromazine has been very helpful in relieving abdominal pains in patients studied by the St Albans group

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8

TOXIPATHIC LIVER DISEASE

THE DESIGNATION *toxipathic* is used in reference to liver disease caused by viruses, bacteria, spirochetes, protozoa, or metazoa; and intoxication from drugs, chemicals, and heavy metals. Morphologic lesions depend on etiology, the quantity of the injurying agent, and the resistance of the host.

The type and location of liver cell necrosis is characteristic. In viral hepatitis it is limited to localized areas in its mild form, and involves the entire lobule in the fulminant variety. Necrosis is accompanied by inflammation and regeneration of liver cells and is followed by collapse of reticular fibers. The parenchyma is replaced by connective tissue containing fibroblasts and inflammatory cells, which may convert a localized process into a diffuse one. With recovery there is a spontaneous subsidence of activity in the connective tissue. After regrowth of the liver cells, mild fibrotic reactions due to condensation of reticular fibers are not evident. Similar reactions have been noted also in infectious mononucleosis and brucellosis.

Cholangiolar injury, which occurs with and without liver cell necrosis, has received considerable attention because it may mimic extrahepatic biliary obstruction. When cholangiolitis is the principal or only manifestation of toxipathic liver disease, clinical recognition is usually difficult. Tests which measure excretory capacity are abnormal whereas those which evaluate

metabolic functions are usually normal Biochemical studies may eliminate parenchymal disease in diagnosis but their results do not distinguish between primary disease of the cholangioles and bile duct alterations secondary to extrahepatic biliary obstruction Initially, only bile stasis is evident, subsequently, a pericholangiolitis may be present This lesion is most commonly present in viral hepatitis, methyl testosterone sensitivity, arsenical intoxication, and chlorpromazine sensitivity Continuation of the pathologic process eventually causes cholangiolitic cirrhosis

VIRAL INFECTIONS

Viral Hepatitis

Epidemiology

Viral hepatitis is caused by two immunologically distinct agents virus "A" *or "I H" (infectious hepatitis) which is responsible for* the naturally occurring disease, and virus "B" or "S H" (serum hepatitis) transmitted by parenteral injection of human blood or its products (1) Neither of these viruses has been recovered although they are transmittible by filtrable agents to human volunteers Viral hepatitis "A" has an incubation period of three to eight weeks and is due to oral-intestinal contamination, although it may be spread by injection Contaminated water and food supplies have been responsible for several epidemics (2) The specific source of the virus is often obscure in patients seen in civilian practice, perhaps due to unrecognized carrier states (3) In our studies, a kitchen worker appeared to be responsible for transmission of the disease in a local monastery, and a pediatric patient was the source of the virus in nine student nurses

Viral hepatitis "A" usually occurs in children and young adults, however, older people also contract the disease Of 155 patients with this form of hepatitis seen in the Jersey City Medical Center, 5, or 3 2 per cent, were over 40 years of age (Fig 35). Clinical recognition is difficult in older patients because of the suspicion of other diseases with a similar clinical picture The disease is more

prevalent in the fall and winter months, the largest number of patients being observed from October to March (Fig 36). This has been attributed to closer contact during cold weather. The sporadic nature of many individual instances of hepatitis and suggestive histories in some patients has led to the suspicion that

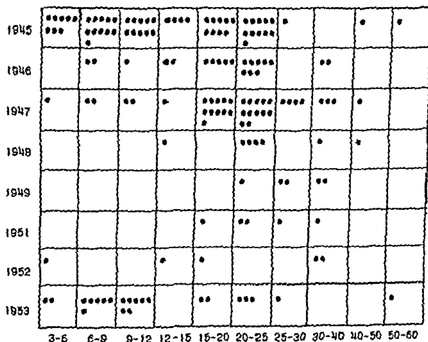


Fig 35 Age incidence of viral hepatitis in Jersey City Medical Center (Leevy, Fialkowski and Gnassi, J Med. Soc New Jersey, 52 237, 1955)

the mosquito may transmit this disease. Epidemiologic studies conducted in our clinic demonstrate potential spread of viral hepatitis by this mechanism but no evidence has been accrued to suggest it is a common method of dissemination. Geographic studies correlated with age and season show relative immunity in areas with previously high attack rates

Viral hepatitis "B" has an incubation period of two to four months and results from contamination with laboratory materials

or the injection of blood or its products Of 29 patients observed with viral hepatitis "B," its source was infusion of plasma or transfusion of blood in 17, injection of infected blood products or use of nonsterile needles and syringes in 10, and laboratory con-

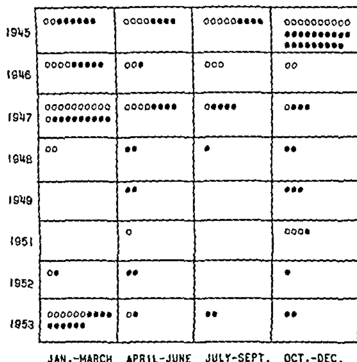


FIG 36 Seasonal incidence of viral hepatitis in Jersey City Medical Center (Leevy, Fialkowski and Gnassi, J Med Soc New Jersey, 52 237, 1955)

tamination in 2. It has been suggested a neonatal form of serum hepatitis results from transmission of the virus through the placenta of mothers who are silent carriers (4) Blood group incompatibility has also been held responsible for this hepatitis which is characterized by large multinucleated giant cells

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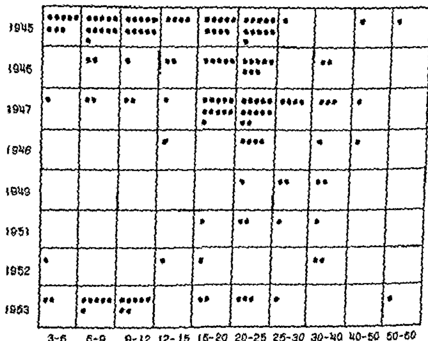
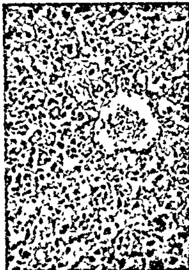


FIG 35. Age incidence of viral hepatitis in Jersey City Medical Center (Leevy, Fialkowski and Gnassi, J Med Soc New Jersey, 52 237, 1955).

the mosquito may transmit this disease Epidemiologic studies conducted in our clinic demonstrate potential spread of viral hepatitis by this mechanism but no evidence has been accrued to suggest it is a common method of dissemination. Geographic studies correlated with age and season show relative immunity in areas with previously high attack rates.

Viral hepatitis "B" has an incubation period of two to four months and results from contamination with laboratory materials







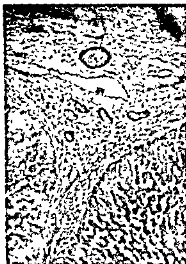


Fig. 37 Viral hepatitis *Top left* Mild viral hepatitis showing eosinophilic coagulative necrosis (repeat biopsy in three months showed normal liver) *Top right* Fulminant viral hepatitis with autolytic necrosis (death occurred in 10 days) *Bottom left* Diffuse fibrosis with active inflammation following viral hepatitis *Bottom right* Postnecrotic scarring following viral hepatitis

MORPHOLOGIC STUDY

Three basic pathologic lesions are encountered in viral hepatitis, depending upon the amount and virulence of the virus, the resistance of the host, and other unknown factors: (a) simple and eosinophilic coagulative necrosis which involves primarily the central areas of the liver lobule, (b) massive or autolytic necrosis; and (c) functional alterations of the cholangioles with or without pericholangiolitis. A combination of these lesions is often present. Fatty changes, present in alcoholics and diabetics, and other preexisting lesions make microscopic interpretation difficult.

In most patients with hepatitis, the hepatic lesion consists of simple and eosinophilic coagulative necrosis. The liver cell nucleus becomes pyknotic and the cytoplasm eosinophilic. A hyaline mass is formed and extruded into the space of Dissé This process is accompanied by intralobular and periportal inflammation which consists chiefly of mononuclear cells with occasional lymphocytes and eosinophiles (Fig 37 top left). Active regeneration of liver cells and Kupffer cells is noted. Serial study shows a decrease in these pathologic changes within 4–6 weeks and return to normal *in two to three months with appropriate therapy (5).* In later stages of viral hepatitis patients with a dietary imbalance have varying amounts of fat on liver biopsy.

A fulminant form of viral hepatitis is associated with massive autolytic central necrosis Death occurs in 10–14 days in most *instances Recognizable liver cells or cords associated with marked* histiocytic reaction are limited to the periphery of the lobule (Fig 37 top right) Bile duct and liver cell regeneration are seen after the fourth day This type of hepatitis occurred in 0 2 per cent of American soldiers with the epidemic form of the disease during World War II. *It seems to develop more often in individuals who* are undernourished, ill, wounded, or fatigued (6a). An epidemic which occurred among menopausal women in Holland suggests an endocrinologic predisposition (6b). No age is immune, infants as well as aged persons have been seen. We have observed 12 patients between the ages of *18* and 63 with fulminant *hepatitis.* All except three succumbed to their disease.

A subacute fulminant form of viral hepatitis is associated with patchy areas of autolytic necrosis and is followed by fibrosis, regeneration of liver cells, and bile ducts. Death occurs in 15–60 days or the patient may survive to develop diffuse fibrosis (Fig 37 bottom left) or postnecrotic scarring (Fig. 37 bottom right) (Fig 38). Those who survive over long periods have progressive inflammation and fibrosis Hepatic fibrosis is seen in the more severe forms of viral hepatitis It is often due to collapse of reticular

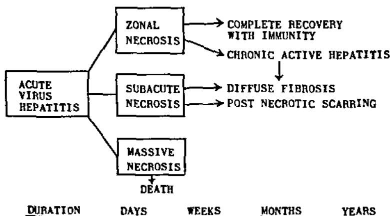


FIG. 38 Clinical course of viral hepatitis

fibers following liver cell destruction There may be complete restitution of the parenchyma when healing occurs and fibrosis is no longer evident on serial biopsy

CASE 10 SUBACUTE FULMINANT HEPATITIS WITH SURVIVAL

Clinical Features V C, a 30-year-old housewife, was admitted with a chief complaint of jaundice associated with anorexia, abdominal fullness, and ease of fatigue Her history was negative for exposure to hepatotoxins and receipt of blood or plasma. A regimen of rest in bed, a high-carbohydrate and high-protein diet, and supplemental vitamins led to the disappearance of symptoms over the ensuing five-month period

Anicteric patients are seen (7), and in the absence of an epidemic, frequently confuse the physician Patients referred to our clinic with a presumptive diagnosis of hepatitis without jaundice have had a variety of nonhepatic diseases

The clinical picture is altered when viral hepatitis occurs with other diseases Gastrointestinal, neuromuscular, hematologic, or metabolic abnormalities resulting from liver dysfunction change the symptoms of the primary illness In our clinic, the chief feature in a diabetic patient was keto-acidosis, a cardiac patient had an increase in fluid retention as the major abnormality, and a patient with peptic ulcer had an exacerbation of intestinal symptoms

Prominent neurologic changes and neuropsychiatric pictures are sometimes seen in viral hepatitis Sensorial changes often accompany severe forms of hepatitis Pathologic studies show lesions of the central nervous system which account for the encephalitic picture, cranial nerve involvement, and peripheral neuritis (8) Neuropsychiatric syndromes may be due to cortical lesions or represent latent emotional disturbances uncovered by the hepatitis Severe abdominal pain occasionally occurs during the course of viral hepatitis and may mimic an acute surgical abdomen

Biochemical Patterns

Biochemical patterns vary in viral hepatitis depending upon the area of the hepatic lobule involved and the severity of the pathologic process In most instances, the entire lobule is affected and both excretory and metabolic function tests are abnormal These patterns can reflect the presence of other diseases Anemia, chronic circulatory congestion and/or malnutrition contribute to observed abnormalities Marked alterations in protein patterns are rarely present High globulin levels are seen with subacute fulminant hepatitis Liver function studies in acute viral hepatitis show bromsulfalein retention in all patients, elevation of serum bilirubin in 90 per cent, positive cephalin flocculation in 85 per cent, decreased cholesterol esters in 75 per cent, decreased glycogen storage capacity in 70 per cent, and elevated thymol

	8/12/54	10/20/54	1/9/51
Hepatomegaly	5 cm	6 cm	2 cm
Splenomegaly	0	0	0
Spider angiomas	0	0	0
Icterus	3+	1+	0
Fluid retention	0	0	0
Hepatic fetor	0	0	0
Sensorial changes	0	0	0
Bleeding esophageal varices	0	0	0
Biochemical study			
Serum bilirubin (mg %)			
Total	24.0	3.2	1.0
Direct	19.0	2.2	0.8
Bromsulfalein retention (%)	71.5	.	8.0
Serum alkaline phosphatase (B.U.)	8.3	4.5	1.9
Total serum cholesterol (mg %)	268	465	325
Cholesterol esters (mg %)	84	207	176
Serum albumin (Gm %)	2.7	3.0	3.1
Serum globulin (Gm %)	4.0	3.2	3.9
Cephalin flocculation	4+	4+	3+
Thymol turbidity (units)	9.5	10.0	5.0
Glycogen storage (mg %)	0	..	21
Histologic study			
Fibrosis	1+		0
Fat	0		0
Regeneration	0		0
Bile stasis	0		0
Inflammation	3+		1+
Necrosis	Autolytic		0
Other	0		0

Clinical Recognition

Clinical recognition of viral hepatitis is possible from the symptom complex and is aided by biochemical liver function studies and needle biopsy of the liver. Diagnosis is facilitated with the appearance of icterus and tender hepatomegaly. It is often difficult in the pre-icteric phase when malaise, weakness, fatigue, fever, headache, anorexia, nausea, and vomiting, and sensorial changes are prominent. Atypical features delay recognition.

found to have bleeding esophageal varices Icterus returned and she was treated with transfusions, diet and prednisone Hemorrhage reoccurred and two years after original onset of jaundice a portacaval shunt was performed The initial portal pressure at the time of surgery (at the New York Hospital) was 380 mm of water It decreased to 150 mm of water after the procedure

	Admission	*After 4 months of therapy*	*After 2 years*
Hepatomegaly	2 cm	0	0
Splenomegaly	3 cm	0	3 cm
Spider angiomas	2+	1+	2+
Icterus	2+	0	2+
Fluid retention	0	0	0
Hepatic fetor	0	0	0
Sensorial changes	0	0	0
Bleeding esophageal varices	0	0	Present
Biochemical study			
Serum bilirubin (mg %)	8 0	0 3	8 1
Urine bile	4+	Neg	
Urine urobilinogen	Neg	1 20	
Serum alkaline phosphatase (B U)	16 0	5 0	8 0
Bromsulfalein retention (%)	41	0	
Total serum cholesterol (mg %)	316	220	316
Cholesterol esters (mg %)	138	140	171
Serum albumin (Gm %)	3 3	4 2	4 2
Serum globulin (Gm %)	2 8	2 6	2 4
Cephalin flocculation	Neg	Neg	Neg
Histologic study			
Fibrosis	0		2+ (Portal)
Fat	0		0
Regeneration	0		2+
Bile stasis	4+	.	0
Infiltration	0	.	2+
Necrosis	0		0
Other	0		0
Pathologic diagnosis	Bile stasis		Cholangiolitic cirrhosis

Three patients observed with advanced cirrhosis which was accompanied by jaundice, hyperphosphatemia, and normal floccula-

turbidity in 70 per cent There is a progressive improvement of biochemical alterations in uncomplicated hepatitis.

Liver cell injury which does not involve the biliary system causes anicteric hepatitis (8). The diagnosis of hepatitis without jaundice depends largely upon biochemical liver function tests It is suspected by history of exposure or contact and should be verified by liver biopsy *unless it occurs as a part of an epidemic.* When the virus affects primarily the biliary system, it produces so-called cholangiolitic hepatitis (9). Biochemical study shows excretory abnormalities without metabolic dysfunction It is difficult to differentiate the ensuing syndromes from extrahepatic biliary obstruction Clinical and laboratory findings do not provide sufficient data for diagnosis, and operative intervention with cholangiography is usually necessary to confirm a diagnosis. We have observed 10 patients with this type of hepatitis Serial biopsy in two patients with this form of hepatitis showed progression to cholangiolitic cirrhosis The final clinical picture was characterized by an enlarged liver, jaundice, evidence of portal hypertension, and xanthomas. Biochemical studies showed elevated serum bilirubin, high serum alkaline phosphatase, hypercholesterolemia, normal flocculation tests, and a normal protein pattern. Histology showed pericholangitis initially, but subsequently there was portal inflammation, proliferation of bile ducts, pseudolobulation, and diffuse fibrosis The following case history is illustrative

Case 11. Cholangiolitic Viral Hepatitis with Transition to Cirrhosis

Clinical Features A S, a 46-year-old housewife, was hospitalized because of jaundice associated with pruritus and epigastric distress. Three months before admission, she had received transfusions during the course of a hysterectomy Examination revealed jaundice, hepatomegaly, and splenomegaly Laboratory tests suggested extrahepatic biliary obstruction, and the patient had an abdominal exploration At laparotomy, the gallbladder and biliary tree were normal Subsequent cholangiographic study showed no abnormality Clinical and laboratory changes returned to normal on a regimen of rest, a high-carbohydrate, moderate-protein, moderate-fat diet, and ACTH The patient remained asymptomatic for a period of one year, when she had melena and was

and other chronic illness complicated by superimposed hepatitis Continued observation is desirable until all stigmas of liver injury have disappeared Full work responsibilities should be instituted gradually and fatigue avoided for a three-month period following recovery Early ambulation decreases the time required for rehabilitation (10) Physical examination and laboratory studies should be repeated 6 months and again 12 months after recovery Criteria for cure of viral hepatitis consist of (a) absence of jaundice, hepatomegaly, and hepatic tenderness, (b) normal bromsulfalein excretion and cephalin-cholesterol flocculation tests, and (c) disappearance of histologic abnormalities

Clinical relapse may occur spontaneously or in patients receiving inadequate therapy It is occasionally noted with an intercurrent illness It is characterized by the return of clinical biochemical, and histologic alterations, and is most often seen in patients who exercise excessively or ingest alcohol in their immediate posticteric phase

Epidemiologic measures are necessary to prevent the spread of viral hepatitis Hospital personnel should be constantly aware of the hazards of this disease and insure normal hygiene measures The need for proper handling of dishes, disposal of feces, and observation of aseptic technics with contaminated needles and syringes cannot be overemphasized Gamma globulin may be valuable for patients exposed to hepatitis I H (13) Viral hepatitis S H is difficult to avoid, but its incidence has been reduced by avoiding pooled plasma Blood donors should be studied for evidence of viral hepatitis with biochemical liver function tests Patients who have recovered from viral hepatitis should not serve as blood donors for a period of at least one year after disappearance of all evidence of liver disease

Infectious Mononucleosis

Infectious mononucleosis is accompanied by hepatic changes similar to those seen in viral hepatitis Needle biopsy frequently exhibits only slight inflammatory changes but may show simple and eosinophilic coagulation necrosis of the liver which is identified with that described for viral hepatitis (14) Necrosis is

tion tests, had a history suggestive of viral hepatitis However, most patients with cholangiolitic cirrhosis of this type have no clear-cut etiologic basis.

Therapy

The natural course of viral hepatitis varies with age, complicating conditions, and general immunity In most instances, recovery is complete within two to three months. Chronic hepatitis with persistence of clinical, biochemical and histologic changes for six months to two years has been noted in 10 per cent of older patients studied in our clinic

The standard form of treatment, including rest, an adequate diet, and general supportive measures as outlined in Chapter Six, is sufficient for mild hepatitis. Bed rest should be encouraged [illegible] who feel

[illegible] viral

[illegible] tients

with a mild form of the disease. A high-protein, high-caloric diet is indicated Parenteral glucose and fructose should be given to patients with anorexia or persistence of poor glycogen stores Treatment with a broad spectrum antibiotic and use of adrenal steroids are helpful in some cases. These drugs should not be employed in treating the usual form of viral hepatitis when recovery occurs spontaneously Supplemental lipotropic agents or testosterone may be desirable to prevent fatty changes of the liver which tend to occur with adrenal steroid therapy (11) Adrenal steroids and ACTH may induce remissions in patients with severe illness, delayed recovery or relapse, and in cholangiolitic hepatitis with prolonged jaundice (12). The response to adrenal steroids given in large doses is occasionally dramatic. High-protein diet, ammonium salts, amino acids, morphine, short-acting barbiturates, and other substances which are detoxified or conjugated by the liver should be avoided in patients who are acutely ill.

Clinical abnormalities due to associated disease states such as anemia, infections, vitamin deficiencies, and water and electrolyte imbalances require treatment. Likewise, attention should be given to basic therapy for heart failure, diabetes, peptic ulcer,

latter form, the heart, liver, and kidney are usually involved In severe cases a hemoglobinemic nephrosis develops which may be associated with oliguria, azotemia, anemia, and finally uremic coma

Extensive acidophilic necrosis of the cytoplasm of the liver cell is noted scattered throughout each lobule, involving part or all of the cytoplasm of individual cells and not disturbing the over-all pattern of the lobules Councilman bodies, which are vacuolated eosinophilic masses of cytoplasm, are characteristic. Inflammatory reaction is minimal The liver lesions reach their peak about the fifth or sixth day of illness after which they undergo rapid resolution and the kidney changes dominate the clinical picture

Biochemical liver function studies show an elevated serum bilirubin In fatal cases hyperbilirubinemia is principally due to an increase in one minute bilirubin Hypoprothrombinemia is constantly present and is responsible for the hemorrhage tendency Routine studies of bleeding time, coagulation time, platelet count, and serum fibrinogen are normal The cephalin flocculation test and thymol turbidity are negative during the first week of illness Renal lesions are accompanied by elevation of blood urea and albuminuria Postmortem specimens are similar to those encountered in viral hepatitis (17) Inability to obtain serial needle biopsies because of bleeding tendency has prevented complete understanding of the course of hepatic alterations in this disease

Clinically, the disease has been divided into a phase of infection characterized by constitutional symptoms for 72 hours, and a phase of intoxication consisting of jaundice, hemorrhage, and albuminuria Jaundice is usually mild Hemorrhage may begin as epistaxis but subsequently marked gastrointestinal bleeding occurs Albuminuria is progressive and accompanied by oliguria and anuria during the terminal phases of the disease There is a bradycardia which is often associated with hypotension and arrhythmia Hypoglycemia, and elevated blood amino acid level, increased blood guanidine, and albuminuria are the principal laboratory findings

accompanied by diffuse infiltration by mononuclear cells, lymphocytes, polymorphonuclear neutrophiles, and eosinophiles Kupffer cells swell and show mitoses Hepatic abnormalities clear within six to eight weeks although they occasionally persist for as long as six to eight months after onset. Leibowitz and Brody observed a patient with infectious mononucleosis and poor nutrition who subsequently developed hepatic cirrhosis (15).

Hepatomegaly, splenomegaly, and jaundice may be the outstanding clinical features of infectious mononucleosis. In these instances, this disease is difficult to distinguish from viral hepatitis. Cervical lymphadenopathy, pharyngitis, atypical lymphocytes, and a positive *heterophile antibody agglutination test* are highly suggestive. However, patients with viral hepatitis may also have abnormal lymphocytes on peripheral blood smears or an elevated *heterophile agglutination titer*.

Biochemical study shows patterns similar to *viral hepatitis*. In a series of 20 patients observed in our clinic with infectious mononucleosis not accompanied by hepatomegaly or jaundice, liver function tests showed an abnormal cephalin flocculation in 80 per cent, elevated thymol turbidity in 70 per cent, and abnormal bromsulfalein excretion in 60 per cent. Liver function tests improved with a decrease in heterophile antibody titer. An occasional patient will have positive cephalin flocculation and thymol turbidity for several months

Patients with evidence of hepatic injury in infectious mononucleosis require intensive therapy until clinical, biochemical, and histologic abnormalities disappear. Treatment consists of a program similar to that employed for viral hepatitis with appropriate rest, diet, and supportive measures

Yellow Fever

Yellow fever is caused by a hepatotropic virus which produces a hepatitis characterized by a prothrombin deficiency and a hemorrhagic diathesis This disease is transmitted by the *Aedes aegypti* mosquito or related strains. Its incidence has been reduced by mosquito control and vaccination (16) Infected persons may develop a subclinical, abortive, or clinical process. In the

cholesterol and esters, elevated serum globulin, and positive flocculation tests

Tuberculosis with involvement of the biliary tract is an anatomic curiosity which is confined to the intrahepatic bile duct area and adjacent liver cells (19) The bile ducts may be involved by retrograde extension from the gastrointestinal tract via the lymphatics, hematogenous spread through the portal system, rupture of a caseating lymph node into a bile duct, or ascending cholangitis

A combination of streptomycin, para-aminosalicylic acid, and isoniazid produces good therapeutic results in hepatic tuberculosis (20). Patients exhibiting hepatomegaly or jaundice should receive intensive therapy The following routine is recommended during the acute phase of the process

1 Streptomycin-dihydrostreptomycin mixture—1 Gm daily

2 Sodium salt of para-aminosalicylic acid—12 Gm daily in divided doses

3 Isoniazid—5 mg / Kg of body weight daily

The streptomycin dosage may be reduced to 1 Gm twice weekly with control of the acute phase

A large solitary tuberculoma may be resected if appropriate chemotherapy is employed before, during, and after surgery

Brucellosis

Although the type and severity of hepatic changes may vary with *Brucella abortus*, *Br melitensis* and *Br suis*, each of these strains causes liver dysfunction Experimental studies by Braude (21) suggest *Brucella* organisms introduced into the body are engulfed by circulating polymorphonuclear leukocytes and Kupffer cells of the liver In turn the Kupffer cells, containing the organisms, aggregate with the epithelioid cells, lymphocytes, histiocytes, and multinucleated giant cells to form a granuloma These granulomas are located in the portal or periportal area and are indistinguishable from those of sarcoidosis, tuberculosis, syphilis, histoplasmosis, or coccidioidomycosis There is usually a gradual reduction in the size of the granuloma with healing and it disappears within a few months without residuum

Diagnosis is established by isolating organisms from the urine, or detecting antibodies in the blood with the mouse protection test and the complement fixation test This disease must be differentiated from Weil's disease and viral hepatitis. No specific therapy is available. Preventive measures include mosquito control and use of vaccines of attenuated virus

Tuberculosis

Hepatomegaly, jaundice, and abnormal biochemical liver function patterns are sometimes present in patients with tuberculosis (18). A *clinical diagnosis of tuberculosis of the liver should* be suspected in patients with pulmonary or gastrointestinal tuberculosis which is accompanied by any of these signs. In most instances, hepatic abnormalities are related to nutritional liver disease Not infrequently, the alcoholic or diabetic patient with poor dietary habits will simultaneously develop hepatic disease and tuberculosis A study of hepatic damage in chronic pulmonary tuberculosis in 60 patients in Delhi, India, showed abnormal biomsulfalein retention in 85 per cent, a positive thymol turbidity in 75 per cent, and a positive cephalin flocculation in 75 per cent *Needle biopsies of the liver were abnormal in 77 per cent of* 59 patients Abnormalities included fatty metamorphosis, necrosis, regeneration of cells, infiltration of chronic inflammatory cells, miliary tubercles, and amyloid (18b)

A diagnosis of miliary tuberculosis with hepatic involvement should be entertained in patients with obscure fever. It is accompanied by seeding of the liver Needle biopsy of the liver is the best method for diagnosis. Skin tests and sputum and gastric cultures for tubercle bacilli are helpful adjuncts. Tubercles are most frequently found in the portal triad, and the finding of caseating *tubercles with giant cells in this area is diagnostic* (Fig 39) Nevertheless, biopsies should be cultured to obtain bacteriologic proof. This is particularly desirable in patients with a tuberculoma since it is often confused with neoplastic disease

Liver function tests in six patients observed by us with miliary tuberculosis involving the liver revealed slightly elevated serum bilirubin, moderate bromsulfalein retention, decreased serum

Prolonged severe *Brucella* hepatitis may be followed by fibrosis. The relationship of brucellosis to eventual fibrosis is not clear, but a case report by MacCullough and Eisele (22) suggests that the necrosis and granulomas which accompany the hepatic disease may be followed by fibroblastic transformation.

Hepatic abnormalities are not conspicuous clinically for they are overshadowed by symptoms incident to brucellosis. We have observed three patients with abdominal pain due to an enlarged liver as a major manifestation of brucellosis. Right upper quadrant pain suggested acute cholecystitis in two of this group. An enlarged spleen may be present and occasionally icterus is noted. Liver function tests often show bromsulfalein retention and positive flocculation tests. There is frequently a leukopenia.

A diagnosis of brucellosis is best established by blood culture and agglutination studies. In the absence of a positive blood culture, culture of material from a liver biopsy may provide bacteriologic proof.

Treatment of brucellosis has been successful with broad spectrum antibiotics. *Brucella* hepatitis is controlled by 0.25 Gm of the tetracyclines (Achromycin, Terramycin) or chloramphenical four times daily given for periods of one to two months in interrupted courses.

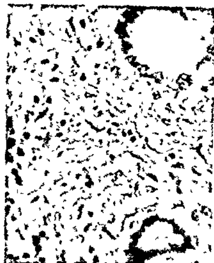
Typhoidal Hepatitis

Typhoid fever is accompanied by biochemical liver function alterations in most instances. A study of these tests in a series of 20 patients with typhoid fever in the Jersey City Medical Center showed hepatocellular changes similar to those seen in pneumonia and other systemic infections. Rarely, the carrier state is due to chronic typhoidal hepatitis. One long-time carrier of typhoid observed in our clinic had persistent positive stool cultures and biochemical evidence of hepatitis despite treatment with Chloramphenicol and removal of a gallbladder from which the typhoid bacillus was cultured.

There are usually few clinical evidences of hepatic disease in typhoid fever. Occasionally, there is liver enlargement or jaundice, which may be due to typhoidal hepatitis or a combina-

Fig 39

Fig 40





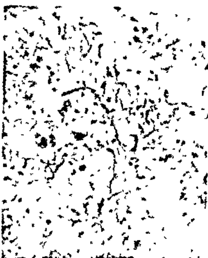




Fig 41

Fig. 42

Fig 39 Tuberculosis of liver showing giant cells
Fig 40 Pyogenic liver abscess
Fig 41 Congenital syphilis showing spirochetes in liver.
Fig 42 Boeck's sarcoidosis

Laboratory studies show a marked leukocytosis, an elevated diaphragm on chest x-ray, and alteration of liver function tests Serum bilirubin, bromsulfalein, and alkaline phosphatase are elevated with and without biliary obstruction. Cholesterol and protein patterns are abnormal in most instances and according to our observations one half of the patients have positive flocculation tests

Therapy consists of a combination of antibiotics including penicillin, streptomycin, and broad spectrum antibiotics such as a tetracycline (Achromycin or Terramycin) chloramphenicol, or erythromycin to control sepsis Surgical drainage is desirable when there is a large solitary pyogenic abscess of the liver

SPIROCHAETAL INFECTIONS

Syphilis of the Liver

Syphilis of the liver is rarely seen in clinical practice today, although many older patients with liver disease have unrelated syphilitic infections Recognition of syphilis as the cause of chronic liver disease is difficult since (a) abnormal serum protein patterns cause false-positive serologic reactions in many patients (use of the antitreponemicidal test eliminates this confusion), (b) alcoholic patients with nutritional liver disease may have late or latent syphilis which may not involve the liver, (c) arsenical therapy for syphilis occasionally produces acute or chronic liver disease (as a result of arsenical intoxication or viral hepatitis, S H), (d) observed histologic alterations in syphilitic liver disease are not specific

Hepatic syphilis may be congenital or acquired (23). The congenital variety is characterized by diffuse fibrosis and marked distortion of the lobular pattern of the liver. Initially, small gummas are found throughout the liver and later coalesce to form large gummas (Fig 41). Although acquired acute syphilitic hepatitis may exist, it has not been unequivocally demonstrated In secondary syphilis the nature of encountered hepatic abnormalities is also not clear. Acquired tertiary syphilis is characterized

tion of hepatitis and nutritional liver disease. Biochemical studies are nonspecific. Liver biopsy shows focal necrosis and inflammation. The diagnosis of typhoid is established by blood cultures, stool cultures, and agglutination studies. Treatment consists of chloramphenicol, antidiarrheal measures, and supportive therapy. Chloramphenicol should be given in an initial dose of 4.0 Gm followed by 2 gm daily until acute symptoms are controlled. A carrier state should be suspected and cholecystectomy undertaken on patients who continue to have positive stools after several periods of adequate chemotherapy.

Pyogenic Liver Abscess

Pyogenic liver abscesses have been rare since the advent of antibiotics. Any organism may be cultured from the abscess cavity although *Escherichia coli*, streptococci, and staphylococci are the common agents. Of 14 patients with pyogenic liver abscess observed in our clinic during the antibiotic era, bacteriologic study revealed *Esch. coli* in 10, *Micrococcus pyogenes* in 2, and *streptococcus faecalis* in 2. Infective organisms may reach the liver from: (a) the portal vein, (b) the hepatic artery, (c) direct extension from the kidney, gallbladder, stomach, or subphrenic area, (d) lymphatic spread, (e) extrahepatic biliary infection, and (f) trauma. In our series of cases, the abscess was secondary to biliary obstruction in six patients, appendicitis in three patients, salpingitis in two patients, diverticulitis in two patients, and subacute bacterial endocarditis in one patient. Abscesses may be single or multiple. There is necrosis of liver cells and an inflammatory reaction is adjacent to the abscess cavity on microscopic examination (Fig. 40). The abscess may reach a large size and involve Glisson's capsule. It occasionally ruptures to produce an empyema, subphrenic abscess, or generalized peritonitis.

Chills and fever are characteristic clinical findings. The liver is tender and hepatic enlargement extends upward as well as subcostally. Varying degrees of icterus are found depending upon the cause and extent of the abscess. Intense icterus is present when a liver abscess is due to extrahepatic biliary obstruction.

Laboratory studies show a marked leukocytosis, an elevated diaphragm on chest x-ray, and alteration of liver function tests Serum bilirubin, bromsulfalein, and alkaline phosphatase are elevated with and without biliary obstruction Cholesterol and protein patterns are abnormal in most instances and according to our observations one half of the patients have positive flocculation tests

Therapy consists of a combination of antibiotics including penicillin, streptomycin, and broad spectrum antibiotics such as a tetracycline (Achromycin or Terramycin) chloramphenicol, or erythromycin to control sepsis Surgical drainage is desirable when there is a large solitary pyogenic abscess of the liver

SPIROCHAETAL INFECTIONS

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by gummas which may be microscopic or large enough to be seen grossly The gummas consist of vascular and perivascular cellular infiltration associated with eosinophilic necrosis and endarteritis Where they heal they contract to form deep scars

A diagnosis of syphilitic liver disease should be entertained where there are signs and symptoms of secondary or tertiary syphilis. It should also be considered in patients with positive serologic tests for syphilis and clinical evidence of liver disease Clinical stigmas are not specific. With tertiary syphilis there is [illegible] the possibility of syphilis of the liver and is, therefore, the most valuable single test (24). Serologic tests are not specific because of frequent false-positive reactions, but they are useful in following the course of therapy Both excretory and metabolic liver dysfunction occurs depending upon the extent and severity of the process

Treatment consists of 12,000,000 units of penicillin given over a 10-day period A repeat course is advisable after several weeks to determine the influence of further therapy on quantitative serologic titers Supplementary measures should include rest, diet, and potassium iodide

Leptospirosis

Leptospira icterohaemorrhagiae, L canicola, L. sejroe, L bataviae, L pomona, and *L grippotyphosa* all produce acute liver damage with jaundice (25). These spirochetes are transmitted through the urine of infected rats, mice, dogs, cats, pigs, foxes, and horses. The organisms live in a warm, damp environment for several days, and contaminate men via the skin or mucous membranes. Weil's disease, which is caused by the *L. icterohaemorrhagiae* and is the most common disease of this group, is most often seen in miners, sewer workers, fish cleaners, and tunnel diggers. *L canicola* occurs among people in contact with infected dogs.

In Weil's disease there are varying degrees of liver cell necrosis,

biliary stasis, and inflammation, depending upon the severity of the infection. Necrosis is usually zonal but may involve the entire lobule. The acute process is followed by regeneration of liver cells and proliferation of Kupffer cells. Many other organs exhibit pathologic changes. Necrosis of the convoluted tubules and interstitial inflammation of the kidneys are characteristic. Skeletal muscles show vacuolation within striated muscles, loss of cellular detail of muscle fibers, and infiltration with histiocytes, polymorphonuclear leukocytes, and plasma cells. Widespread capillary damage results in a bleeding tendency which leads to hemorrhage into the skin, pleura, peritoneum, the gastrointestinal tract, kidney or adrenals. There may be an associated myocarditis and meningitis.

Clinical features depend upon the anatomic location of lesions, and the stage of the disease. There is usually a sudden onset of fever, prostration, headache, muscle pain, and conjunctivitis with subsequent development of jaundice and skin hemorrhage. Initial examination reveals an elevated temperature, muscle tenderness, and purpura followed by icterus, an enlarged tender liver, oliguria or anuria, and signs of central nervous system involvement. During the first week of illness, *Leptospira* are found in the blood stream and may be identified by darkfield examination, culture, or animal innoculation. Injection of 5 cc of blood intraperitoneally into a young guinea pig permits a positive diagnosis. The animal dies after a period of 10–14 days and autopsy reveals *Leptospira* throughout the liver, kidneys, and other organs. In the first phase of the disease, there is leukocytosis, moderate elevation of blood urea, and spinal fluid pleocytosis. In the second phase, Leptospira appear in the urine. Organisms may be cultured from the urine after the tenth day of illness.

Specific antibodies appear in the serum and reach a diagnostic level of 1:300 or more between the fourteenth and twenty-first day of illness. During this interval, laboratory abnormalities include an anemia, leukocytosis, albuminuria, azotemia, and abnormal liver function tests.

There are marked variations in the clinical picture. A patient observed by us had mental changes as the primary clinical abnormality throughout her illness. A laboratory diagnosis is based upon *Leptospira* in the blood or urine, or a high agglutination titer Needle biopsy of the liver or a muscle biopsy are helpful adjuncts. Leptospirosis icterohaemorrhagica is differentiated from other leptospiral diseases by agglutination reactions. (26)

Penicillin and tetracyclines (Achromycin and Terramycin) both seem to favorably influence the course of Weil's disease although they are not specific (27). These agents should be used in large doses in acutely ill patients. Improvement usually begins during the third week of illness and is followed by a rapid disappearance of clinical and laboratory abnormalities.

AMOEBIASIS

Hepatic complications are noted in approximately 8 per cent of the patients with amoebiasis. *Endamoeba histolytica* spreads from a focal infection in the bowel wall via the small radicles of the portal system and enters the parenchyma of the liver to produce localized liquefaction necrosis. Sequelae depend upon the number and virulence of the parasites, and host immunity. The resulting small lesions coalesce and cause an abscess formation Subsequently the cavity is surrounded by a thick capsule Chronic abscessess contain a reddish-brown fluid unless they become secondarily infected with pyogenic organisms (28). Abscesses are usually located in the right lobe and are solitary in two thirds of the patients. Occasionally they rupture into the pleural cavity or abdomen. A thrombosis of the portal veins also caused by the amoebae sometimes occurs.

Recognition of amoebic hepatitis may be difficult because of the lack of specific signs and symptoms. Hepatomegaly, hepatic tenderness, leukocytosis, abnormal liver function tests and laboratory evidence of colonic amoebiasis are suggestive Needle biopsy of the liver is usually normal and this has raised the question of whether the clinical syndrome of amoebic hepatitis is not due to non-specific intestinal ulceration (28b). A diagnosis of this disease

is justifiable when there is disappearance of clinical and biochemical abnormalities of the liver with appropriate chemotherapy for amoebiasis Criteria for a diagnosis of amoebic liver abscess are more definite

Right upper quadrant pain, chills, fever, and weight loss in a patient who has had diarrhea are characteristic complaints Chest and scapular pain are often present and may be associated with cough Physical abnormalities include compression tenderness of the liver, hepatomegaly, and an elevated right diaphragm Subdiaphragmatic irritation or rupture of an abscess into the pleural cavity cause pulmonary signs and symptoms An x-ray of the chest shows elevation of the right diaphragm which is sometimes accompanied by a pleural effusion The white blood cell count may be normal but is usually between 15,000 and 20,000 Stools are positive for amoebae in one half of the cases The parasite may also be recovered from material aspirated from the liver The complement fixation test is sometimes helpful in establishing a diagnosis Liver function tests are not of much value They are usually normal but may show an elevated serum alkaline phosphatase, bromsulfalein retention, or a positive cephalin flocculation test

The differential diagnosis includes disorders which cause fever and right upper quadrant pain Empyema of the gallbladder, subphrenic abscess, metastatic carcinoma to the liver, perinephritic abscess, and acute hepatic vein thrombosis may simulate liver abscess After establishing a diagnosis of liver abscess, an equally formidable task consists of deciding whether the abscess is pyogenic or amoebic in origin Malaria and other parasitic infestations may be present to complicate the clinical picture The following case history illustrates some of the clinical and laboratory features of amoebic liver abscess

Case 12 Amoebic Abscess of the Liver

Clinical Features C D., a 59-year-old tailor, was hospitalized because of cough, fever, weakness, weight loss of 40 pounds, diarrhea, and nervousness He had been treated during the preceding two years with antithyroid medication Physical examination revealed marked

malnutrition, temperature 101°, enlarged tender liver, auricular fibrillation, and jaundice. A chest x-ray showed a right hydrothorax and elevated diaphragm on the right, thoracentesis yielded 100 cc of straw-colored fluid. A clinical diagnosis of metastatic malignancy was entertained until a liver biopsy revealed evidence of an abscess. Aspiration of the liver was then undertaken and 1000 cc. of reddish-brown pus was removed. A complement fixation test was positive for amoebiasis. The patient was treated with 1 gm of emetine intramuscularly daily for 10 days followed by a course of chloroquine and diiodohydroxyquin. He became asymptomatic and all laboratory and biochemical studies returned to normal.

	Admission	*3 wks later*	*6 mos later*
Hepatomegaly	2 cm		0
Splenomegaly	1 cm		0
Spider angiomas	0		0
Icterus	2+		0
Fluid retention	1+		0
Hepatic fetor	0		0
Sensorial changes	0		0
Bleeding esophageal varices	0		0
Biochemical study			
Serum bilirubin (mg %)	15 6	1 8	0 6
Total serum cholesterol (mg %)	56	171	226
Cholesterol esters (mg %)	16	123	111
Serum albumin (Gm %)	2 1	1 6	4 2
Serum globulin (Gm %)	4 1	4 6	3 1
Cephalin flocculation	4+	3+	1+
White blood cell count	17,200	11,250	8,200
Histologic study			
Fibrosis	0		
Fat	0		
Regeneration	0		
Bile stasis	1+		
Inflammation	4+		
Necrosis	2+		
Other	0		
Pathologic diagnosis	Liver abscess		

made by use
studies The
methods, has

been shortened by six weeks Although needle biopsy is contraindicated in suspected liver abscess it may be a useful tool It was employed on only 1 (6 per cent) of 15 patients who were proved to have amoebic liver abscess However, it was used on several patients in whom abscess was suspected, and it revealed the presence of another disease

Chloroquine diphosphate in doses of 0 6 Gm daily for two days followed by 0 3 gm daily for 12–19 days is the treatment of choice If there is no response, patients may be given a tetracycline (Achromycin or Terramycin) in doses of 250 mg four times daily or emetine hydrochloride in doses of 60 mg intramuscularly each day for 10 days Blood pressure readings should be obtained twice daily, and electrocardiograms once weekly in patients receiving emetine

A combination of chemotherapy and hepatic aspiration is necessary in amoebic liver abscess Aspiration may be facilitated by surgical exploration Closed aspiration is sufficient in some instances However, where there is difficulty in localizing the abscess, surgery is advisable Chloroquine, administered in the same dosage as in amoebic hepatitis, is the drug of choice in our experience Good results may also be obtained with emetine in doses of 60 mg daily intramuscularly, notwithstanding its myocardial toxicity and potential development of drug refractoriness Tetracycline derivatives are useful in amoebic abscess with secondary bacterial infection Aspiration of the liver should be performed using the following technic

1 SITE OF ASPIRATION The point of maximal tenderness is the preferable area of entry In our experience, this has most frequently been between the eighth and tenth interspaces in the posterior axillary line If there is no specific area of tenderness, the choice of a site depends upon the area of greatest dullness or is determined by radiologic studies A limited experience suggests the liver scanning technic with iodinated human serum albumin (see Chapter Three) is not helpful in localizing amoebic abscess Subcostal aspiration of the liver is preferable when enlargement is principally intraabdominal

2 PROCEDURE (a) Infiltrate skin, subcutaneous tissues and muscles to the capsule of the liver with 1% procaine (b) Introduce a #15 or #16 needle and withdraw as much material as possible

Streptokinase-streptodornase may be helpful in liquefying the exudate in amoebic abscess. This material appeared to be beneficial to a patient with a sinus tract in which drainage stopped spontaneously. In most instances, we have introduced emetine hydrochloride into the abscess cavity at the end of the aspiration

A course of anti-amoebic drugs designed to rid the colon of cysts of amoebae is desirable following control of the hepatic lesions. Diodoquin is useful for this purpose and should be given in doses of 0 63 gm. four times a day for 20 days Chiniofon, Carbarsone, and the tetracyclines (Terramycin) appear to be equally effective.

Prognosis is good with early therapy. Among a series of 15 patients treated over a seven year period, one with multiple liver abscesses developed diffuse fibrosis of the liver, and three died with uncontrolled abscess formation. Two of these patients received surgery for a suspected surgical disease, and one had a large abscess with marked sepsis which was refractory to all medicinal agents plus aspiration.

RELAPSING FEVER

Relapsing fever may be responsible for jaundice, a hemorrhagic tendency, liver enlargement, and splenomegaly. It is caused by *Borrelia recurrentis* transmitted by the louse and *Bor. novyi* and *Bor. duttoni* transmitted by the tick. An abrupt onset of chills and fever is the first manifestation of the disease. The diagnosis is established by demonstrating a spirochetemia during the early phase of the disease, and positive agglutination or complement fixation tests later (29). Treatment consists of 1,200,000 units or more of penicillin each day until signs and symptoms disappear.

METAZOAL INFECTIONS OF THE LIVER

Echinococcosis

Echinococcosis is an endemic disease caused by the tapeworm *Taenia echinococcus* which produces cysts in the liver and other organs. The liver is involved in three fourths of the patients with this disease. Man becomes infected by contact with dogs,

sheep, hogs, and cows infected with ova of the tapeworm. The ova are ingested by men and burrow through the stomach wall to enter the portal system and the liver. Hepatic cysts form and collect fluid which may become secondarily infected The cysts may expand and compress the liver cells or bile ducts

The appearance of this cystic mass is often the earliest clinical sign of echinococcosis. Jaundice is occasionally present due to bile duct compression Presenting symptoms are related to rupture of a cyst with signs of an acute abdomen and an anaphylactoid reaction.

Routine abdominal x-rays demonstrate the cyst when its wall is calcified The disease should be suspected in patients who exhibit a cystic mass of the liver and eosinophilia It is proven by finding scolices in the stools, sputum, or gastric contents and by skin tests, the complement fixation test, or precipitation test Subcutaneous injection of commercially available hydatid fluid (Casoni reaction) in a patient with echinococcosis will produce a wheal which is surrounded by an erythematous zone within 10–20 minutes (30)

Therapy for echinococcosis consists of control of symptoms produced by the cysts The treatment of choice is surgical closure of cysts after evacuating their contents by aspiration One per cent formalin and alcohol may sterilize the remaining cavity and prevent contamination when complete removal is not possible The disease is often so widespread that this type of therapy is only palliative

Schistosomiasis

Schistosomiasis is a common disease found in many tropical areas of the world It has become a frequent medical problem in the United States because of the large number of Puerto Rican immigrants. Invasion of the liver occurs in the life cycle of all three species of *Schistosomum S mansoni*, *S japonicum*, and *S haematobium* In the natural history of these parasites, their ova are excreted in the feces (*S mansoni*, *S japonicum*) or urine (*S haematobium*) and rupture in water to liberate a *miracidium* which penetrates a suitable snail *Cercaria* develop

after one to two months and leave the snail to penetrate the skin and enter the lymphatic system of people bathing in contaminated water. In the body, they are carried to the capillaries of the lungs, enter the systemic circulation, and lodge in the mesenteric and portal veins Mature worms migrate out of the liver. Ova of the *S. mansoni* lodge in the colon and rectum, *S. japonicum* in the small intestine and rectum, and *S. haematobium* in the venous plexus of the bladder and the pelvis.

Schistosomum produce granulomatous lesions in the liver which may contain an ovum or calcified chitinous material There may be periportal fibrosis which in its severe stage is associated with calcification of vessels leading to the descriptive term "pipe stem cirrhosis" This cirrhosis has been attributed to concomitant nutritional deficiency (31), and to the end results of continued oviposition in portal areas, and the reaction thereto, over a period of many years

Schistosomiasis is an important factor in the pathogenesis of hepatic cirrhosis in Puerto Rico, being the causative agent in 19 7 per cent of 112 reported cases (31b) Bilharzial cirrhosis occurs predominantly between 20 and 40 years of age, and is associated with a high incidence of esophageal varices and splenomegaly The young age group is attributed to the fact the infection is acquired during childhood while river bathing, portal hypertension is related to the distortion of intrahepatic tributaries of the portal vein which results from the vasculitis and portal fibrosis following deposition of *S. mansoni* ova in the portal vein radicles.

There is little evidence of hepatic involvement in the early stages of schistosomiasis Nausea, vomiting, diarrhea, and abdominal pain dominate the clinical picture and are accompanied by chills, fever, a dermatitis, and eosinophilia Subsequently, one notes an enlarged liver and spleen, and in some instances, jaundice and fluid accumulation. Biochemical studies are usually normal or show slight bromsulfalein retention or positive flocculation tests (32). Liver biopsy is diagnostic when the specimen contains whole eggs or fragments of shells. A positive diagnosis depends upon identification of ova and has to be made usually

by biopsy of the rectal mucosa for *S mansoni* and *S japonicum*, and of the bladder mucosa for *S. haematobium*. An intradermal test, complement fixation test, and precipitation test are available and constitute valuable adjuncts in skilled hands

Therapy consists of stibophen or tartar emetic, both may be hepatotoxic agents Stibophen should be given in doses of 1 5 cc followed by 3 5 cc the next day and 5 cc. every other day until 100 cc have been given

Clonorchiasis

Hepatic involvement is characteristic of clonorchiasis (liver fluke) (33) Ova of the fluke are ingested by a snail which serves as an intermediate host. After the egg hatches, it matures into cercariae which enter the body of fish and encyst as metacercariae Cercariae encyst in the duodenum and enter the bile ducts when the fish is eaten by man Affected bile ducts become dilated and their walls thicken in response to an inflammatory process This is accompanied by an increase in periportal connective tissue and eventually causes biliary fibrosis or cirrhosis

Clinical features depend upon the severity and longevity of the infection There is usually an eosinophilia and a leukocytosis Evidence of hepatic disease includes liver enlargement, jaundice, and fluid retention Biochemical liver tests show impairment of excretory function The diagnosis is established by finding the ovum in the stools or on duodenal drainage. Therapy is not specific and consists of giving gentian violet, 0 06 Gm three times daily before meals for one month, and repeating the course after a two-week rest period

Sarcoidosis

Sarcoidosis involves the liver in a large percentage of patients Rarely is the hepatic lesion of clinical importance Finding the characteristic histologic lesion of the liver facilitates diagnosing Boeck's sarcoid (34) Serial biopsies show parenchymatous degeneration and an exudative reaction followed by appearance of lymphocytes, histiocytes, giant cells, and epithelioid cells

after one to two months and leave the snail to penetrate the skin and enter the lymphatic system of people bathing in contaminated water In the body, they are carried to the capillaries of the lungs, enter the systemic circulation, and lodge in the mesenteric and portal veins Mature worms migrate out of the liver. Ova of the S *mansoni* lodge in the colon and rectum, S. *japonicum* in the small intestine and rectum, and S. *haematobium* in the venous plexus of the bladder and the pelvis

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plasmic destruction (35) Hypersensitivity reactions may consist of an anaphalactoid type of reaction, or produce vascular alterations with secondary hepatic changes (36)

A careful history is necessary to differentiate toxic hepatitis from that caused by viral or other infective agents Clinical findings depend upon the general status of the patient, the type and amount of the injurious agent, and effects of the noxious substance on other organ systems Concomitant renal, central nervous system, dermatologic, bone marrow, pulmonary, or myocardial lesions are frequently present to produce additional signs and symptoms Biochemical study shows fewer abnormalities in metabolic tests than in viral hepatitis Morphologic study is helpful in the differential diagnosis Toxic necrosis is associated with fatty changes and a low grade mesenchymal reaction in contradistinction to minimum fatty metamorphosis and a marked reticuloendothelial reaction in viral hepatitis Anatomic criteria are not helpful in diagnosis in the healing or fibrotic stage of toxic liver injury.

Table 16 Drugs and Chemicals Reported as Causing Toxiopathic Liver Disease

Alloxan	Copper	Nitrobenzene
Amanita toxin	DDT	Para-aminosulfonic acid
Antimony	Diethylstilbesterol	Phenylbutazone
Arsenic	Dilantin sodium	(Butazolidin)
Atabrine	Dinitrophenol	Phenylhydrazine
Aureomycin	Ether	Phosphorus
Avertin	Favabean	Propylthiouracil
Bismuth	Fowler's solution	Stilbamidine
Carbon disulfide	Gold	Sulfonamides
Carbon tetrachloride	Tannic acid	Synthalin
Chloramphenicol	Iodoform	Terramycin
Chloroform	Lead	Tetrachlorethane
Chlorpromazine	Manganese	Tetraiodophenothalein
Chromium	Mercury	Thiouracil
Cinchophen	Mesantoin	Trinitrophenol
Colchicine	Methyl testosterone	Urethane

A complete description of the various substances which have been found to be hepatotoxic, or even those with which the author has had personal experience would be too lengthy Accordingly, the reader is referred to standard texts for detailed description of

which form a granuloma (Fig. 42). Giant cells may show a dark staining laminated material (Schaumann inclusion body). Proliferation of fibrous connective tissue occurs in the area of the granuloma and it could cause distortion of the hepatic lobule

Studies of patients in whom pulmonary sarcoidosis is found on routine chest x-ray often show no clinical, biochemical, or histologic abnormalities to indicate hepatic involvement Moderately advanced sarcoidosis may not present clinical evidence of hepatic involvement, but biochemical tests showed a relatively high incidence of bromsulfalein retention and serum protein alterations, and needle biopsy was positive in 80 per cent of the cases studied by the author in military personnel. In advanced stages, the liver and spleen are frequently enlarged, and occasionally jaundice and evidence of portal hypertension are present Jaundice may be related to hemolysis, hepatocellular dysfunction, or extrahepatic obstruction from lymph node enlargement. Biochemical liver function tests demonstrate abnormal serum protein patterns, positive flocculation tests, and bromsulfalein retention. Electrophoretic analysis of plasma proteins shows an elevation of gamma globulin and some elevation of beta globulin. Alkaline phosphatase is occasionally elevated in both nonicteric and icteric patients. The Nickerson-Kveim test, needle biopsy of the liver, or biopsy of a lymph node correlated with clinical findings provide material for a diagnosis of sarcoidosis although none of these tests is specific. Treatment consists of supportive measures. Adrenal steroids are indicated when there is severe hepatic involvement, although some evidence suggests corticoid therapy may accelerate hepatic fibrosis.

CHEMICAL INTOXICATIONS

Liver injury, acute and chronic, is caused by a variety of chemicals (Table 16) Chemicals cause liver injury through a direct toxic effect or as a result of a hypersensitivity reaction. Toxicity has been related to interference with nutritional requirements, inactivation of essential enzyme systems, and direct proto-

plasmic destruction (35) Hypersensitivity reactions may consist of an anaphalactoid type of reaction, or produce vascular alterations with secondary hepatic changes (36).

A careful history is necessary to differentiate toxic hepatitis from that caused by viral or other infective agents Clinical findings depend upon the general status of the patient, the type and amount of the injurious agent, and effects of the noxious substance on other organ systems. Concomitant renal, central nervous system, dermatologic, bone marrow, pulmonary, or myocardial lesions are frequently present to produce additional signs and symptoms Biochemical study shows fewer abnormalities in metabolic tests than in viral hepatitis Morphologic study is helpful in the differential diagnosis Toxic necrosis is associated with fatty changes and a low grade mesenchymal reaction in contradistinction to minimum fatty metamorphosis and a marked reticuloendothelial reaction in viral hepatitis Anatomic criteria are not helpful in diagnosis in the healing or fibrotic stage of toxic liver injury.

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A complete description of the various substances which have been found to be hepatotoxic, or even those with which the author has had personal experience would be too lengthy Accordingly, the reader is referred to standard texts for detailed description of

toxic effects of most of the agents mentioned in Table 16 Drugs and industrial agents which have produced hepatic injury most frequently in our experience in a large municipal hospital will be reviewed Early and prompt treatment is an important aspect of control of liver injury due to chemicals It is necessary to eliminate contact with the injurious agent, provide any specific antidote which is available, and give general supportive measures including rest, diet, and symptomatic therapy.

1. Antibacterial agents

Sulfonamides produce liver function abnormalities and focal inflammation on biopsy in an occasional patient. This is usually accompanied by other evidence of toxicity. Rarely, hepatic injury may be the major abnormality, massive necrosis resulting from a sensitivity type of reaction (37). Therapy consists of stopping the sulfonamide and administering adrenal steroids.

Tetracycline derivatives given intravenously may cause jaundice, hepatomegaly, liver function abnormalities, and fatty vacuolation on biopsy (38). The hepatotoxic effect of these drugs appears to be related to a chemical effect although they may cause injury by interfering with some essential metabolic process. Despite reported ill effects of these antibiotics it is desirable to use them in treating patients with severe liver failure, as indicated in Chapter 6

Isoniazid, para-aminosalicylic acid, and pyrazinamide have each produced hepatic dysfunction, jaundice, and hepatomegaly when employed in the chemotherapy of tuberculosis. Hepatic injury occurs in 3 per cent of patients receiving a daily dose of 40 mg. Kg. of pyrazinamide and may cause death (39). When these drugs are used it is necessary to consider viral hepatitis and tuberculous involvement of the liver in the differential diagnosis. Therapy consists of withdrawing the drug and providing supportive measures

Arsenical intoxication results from oral or intravenous arsenic preparations (40). The most common chronic liver injury occurs in patients who have received arsenicals for syphilis. Oral arseni-

cals have led to fatty liver and cirrhosis Intravenous arsenicals produce cholangiolar or diffuse hepatitis, either of which may be followed by hepatic fibrosis Decision that arsenicals are responsible for a hepatic lesion is difficult. The possibility of nutritional liver injury is present, and viral hepatitis may be responsible for the observed hepatic lesion following intravenous arsenical therapy Diagnosis is suggested by clinical evidence of arsenic toxicity such as exfoliative dermatitis, skin pigmentation, and nasal septal perforation There is an increased excretion of arsenic in the urine, the normal value being 0 017 mg 100 cc of urine Treatment in the acute phase of arsenic intoxication consists of BAL The drug should be given cautiously because of its hepatotoxic potential In chronic liver injury, treatment is supportive

2. Sedatives

Barbiturates may, rarely, cause liver dysfunction in patients who develop a hypersensitivity to them Frank hepatitis with jaundice, an enlarged liver, abnormal function tests, and necrosis of liver cells has been reported (41)

All of the available antiepileptic drugs have been noted to be hepatotoxic in individual patients Phenurone causes hepatitis in 2 per cent of patients, and in many instances produces a fatal reaction (42) Hepatic dysfunction is a rare complication of Tridione therapy (43), and it is even less common in patients receiving Dilantin and Mesantoin

Chlorpromazine occasionally produces a cholangiolar hepatitis characterized by hepatomegaly, jaundice, predominant alteration of excretory liver function tests, and bile stasis with spottly inflammatory cells in the liver lobules on histologic study (44). Symptoms include pruritis, nausea, vomiting, diarrhea, fever, malaise, and/or weight loss Biochemical studies show an elevated serum bilirubin, increased alkaline phosphatase, hypercholesterolemia, bromsulfalein retention, and normal flocculation tests, protein patterns, and cholesterol esters Needle biopsy shows bile plugs in biliary canaliculi, parenchymal cell pigment, and no significant inflammation Clinical features usually occur while the

patient is receiving the drug but may develop after it has been discontinued Therapy consists of withdrawal of the offending agent and use of corticotropin or adrenal steroids.

3. Antiarthritic drugs

Cinchophen is notably hepatoxic and side reactions have led to its discontinuation as a routine measure for arthritis. Hepatic damage is usually noted after several weeks or months of treatment There is usually fairly extensive necrosis of parenchymal cells with varying degrees of inflammation (45). Gold therapy is occasionally complicated by a hepatitis which has been attributed to a virus. We have observed patients with hepatitis who received gold for rheumatoid arthritis, where autoclaved syringes were used for the injected materials and there was no suggestion of exposure to viral hepatitis. Similar necrosis of the liver has occurred in patients with arthritis treated with phenylbutazone (46). Varying clinical and biochemical abnormalities are present. Therapy consists of withdrawal of the cinchophen, gold, or butazolidin, and of administration of supportive measures.

4. Anesthetic agents

All anesthetic agents cause minor changes in liver function tests (47) and it is therefore necessary to select those which are least hepatotoxic when patients with liver disease are subjected to surgery Chloroform is the most toxic of the clinically used anesthetics It causes centrilobular necrosis with an inflammatory reaction which may be followed by fibrosis. Tribromethanol, diethyl ether, divinyl ether, and cyclopropane may produce significant biochemical liver function alterations

5. Miscellaneous drugs

Many other drugs cause hepatic damage in man. Patients receiving antithyroid drugs—thiouracil (48), propylthiouracil (49), or tapazole (50)—occasionally develop a hepatitis which is similar to that seen in chlorpromazine therapy. Methyl testosterone also produces a cholangiolar type of hepatitis with clinical, biochemical, and histologic features suggesting obstructive jaundice

(51) Urethane (52), atabrine (53), and dinitrophenol (54) are other potentially hepatotoxic drugs which are widely used in clinical practice.

6. Industrial agents

Accidental or industrial contact with carbon tetrachloride, phosphorous, tetrachlorethane, nitrobenzene, arsine, trinitrotoluene, D D T, naphthalene, beryllium, and many other agents cause clinical, biochemical, and histologic evidence of liver disease Of this group carbon tetrachloride has been the most common cause of toxic liver injury in our experience Toxicity occurs most often when it is used as a solvent or cleaning fluid in an improperly ventilated area (55) Carbon tetrachloride produces hepatic and renal lesions The liver lesion is characterized by centrilobular necrosis which is accompanied by fatty metamorphosis Diffuse hepatic fibrosis may develop in patients who do not succumb to the acute process The kidney lesion consists of tubular necrosis and is often the major pathologic abnormality Jaundice, hepatomegaly, hematuria, oliguria, and anemia are the chief clinical abnormalities Laboratory studies show moderate to severe liver functional changes and chemical characteristics of renal insufficiency Therapy consists of supportive and symptomatic measures Little can be done to alter the progressive downhill course in the presence of severe hepatic or renal injury

Intravenous methionine, advocated by some, has not been beneficial in our experience It is necessary to recognize and promptly treat serum potassium disturbances in patients with progressive renal failure Intravenous glucose and calcium may be helpful in control of hyperkalemia Artificial dialysis may also be necessary Acidemia should be treated with sodium salts where there is a low total circulating sodium

Berylliosis may be accompanied by centrilobular necrosis, granulomatosis, and/or fatty metamorphosis, all of which contribute to fibroblastic transformation of the liver (56) Tetrachlorethane produces necrosis and fatty changes of the liver which are frequently associated with renal alterations Phosphorus causes a severe degree of necrosis which is usually fatal

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(57). DDT (58), napthalene (59), and TNT (60) may produce necrosis, fatty change, and inflammation of the liver with varying clinical and biochemical abnormalities

MUSHROOM POISONING

Amanita phalloides produces phallin which causes hemolysis, and amanito-toxin which causes necrosis and fatty vacuolation of liver cells Massive hepatic necrosis leading to an early demise characterizes a large number of cases of ingestion of mushrooms containing this poison (61) Gastrointestinal symptoms are followed by jaundice, hepatomegaly, splenomegaly, and signs of renal and central nervous system injury The liver lesion may be followed by fibrosis but it usually heals without residium

ECLAMPSIA

Eclampsia is frequently associated with peripheral hemorrhagic necrosis of liver lobules. Varying amounts of fat may be present *The cause of the lesion is not known but it is presumably related* to vascular alterations which characterize toxemia of pregnancy. Studies by Dr Nicholas Alter at the Margaret Hague Maternity Hospital in Jersey City have shown the lesion to be frequently absent in proven instances of this disease. Clinical evaluation may reveal jaundice, hepatomegaly, and liver function changes Viral hepatitis, nutritional liver disease, and toxic hepatitis must be considered in the differential diagnosis.

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9

THE LIVER IN CIRCULATORY DISTURBANCES

CIRCULATORY congestion or anoxia seriously interferes with liver cell function by altering normal oxygen uptake Oxygen must be supplied to the parenchymal cells at a sufficiently high tension Low levels of oxygen saturation of hepatic venous blood leads to very low oxygen tensions in the centrilobular cells of the liver. Minor degrees of anoxia are accompanied by vacuolation of the liver cells, and moderate to severe anoxia produces central necrosis It has been suggested that interference with oxygenation is the common denominator responsible for all necrosis of liver cells (1). Swelling of parenchymal cells causes ischemia in acute liver injury, and architectural distortion of the hepatic lobule leads to circulatory disturbances in chronic hepatic disease

Passive Congestion and Its Sequelae

Reconstruction of the events leading to hepatic abnormalities in congestive heart failure has been difficult because of inability to obtain long-term follow-up studies in most patients with chronic circulatory congestion (Fig 43) Right sided heart failure is char-

52 MEACHAM, G C, TILLOTSON, F. W., and HEINLE, R. W. Liver damage after prolonged urethane therapy *Am. J. Clin Path* 22 22, 1952

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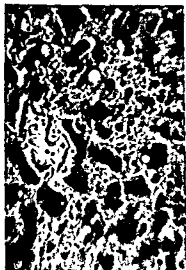






Fig 44 The liver in congestive heart failure *Top left* Passive congestion *Top right* Centrilobular necrosis with inflammation *Bottom* Pericentral vein fibrosis.

acterized by passive congestion which is accompanied by serous exudation in the space of Dissé (Fig 44 top left) Necrosis of centrilobular cells develops with severe anoxia (Fig. 44 top right). If this lesion heals, there is condensation of the reticular stroma, and recurrent episodes of congestive failure lead to pericentral vein fibrosis (Fig 44 bottom) (2).

The severity of congestive heart failure and previous dietary habits are important determinants of anatomic changes Histologic alterations cannot be related to the type of heart disease, heart

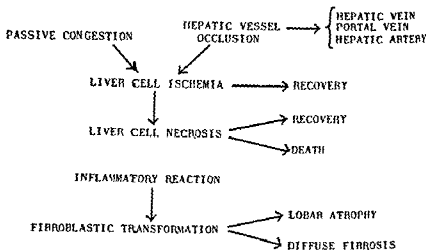


FIG. 43 Circulatory factors in evolution of chronic liver injury

size, electrocardiographic findings, or presence of arrhythmia Hepatic blood flow as measured by the bromsulfalein extraction method is reduced in chronic circulatory congestion (3). Exercise causes a further reduction in hepatic blood flow and a marked increase of hepatic oxygen A-V difference. This results in a very low oxygen saturation of hepatic venous blood and contributes to functional and morphologic abnormalities (4).

The following case history illustrates clinical, biochemical, and histologic changes which occur with congestive heart failure.

Case 13 Development of Centrilobular Fibrosis in Circulatory Congestion

Clinical Features. A.K., a 49-year-old laborer, was hospitalized for dyspnea and ankle edema. Examination revealed rheumatic heart disease with an enlarged heart, mitral stenosis, and auricular fibrillation. His liver was enlarged 6 cm. below the costal margin. On a regimen of rest, digitoxin, sodium restriction, and mercurial diuretics, fluid retention disappeared but tender hepatomegaly persisted. The patient was maintained on a cardiac regimen but had repeated bouts of lung edema. Restudy one year later showed marked cyanosis, dyspnea, right upper quadrant pain, and an enlarged liver 7 cm. below the costal margin. The cardiac findings were not changed.

	Initial study	*1 year later*
Biochemical study		
Serum bilirubin (mg. %)	2.6	2.8
Bromsulfalein (%)	16.5	23.5
Total serum cholesterol (mg. %)	144	182
Cholesterol esters (mg. %)	101	92
Serum albumin (Gm. %)	3.27	3.0
Serum globulin (Gm. %)	4.2	4.2
Cephalin flocculation	Neg.	2+
Thymol turbidity (units)	3.0	3.0
Histologic study		
Fibrosis	0	1+
Fat	0	0
Regeneration	1+	1+
Bile stasis	0	0
Infiltration	0	1+
Necrosis	0	0
Other (congestion)	3+	3+

Morphologic study of the liver in heart failure shows varying degrees of congestion of the sinusoids. Mild to moderate congestion is not accompanied by cellular changes, and stigmas of heart failure may be absent on histologic study, for much of the blood is pressed out by the needle biopsy technic. Sclerosis of the hepatic vessels results from intrahepatic hypertension in patients with

bilirubin in 40 per cent, a positive cephalin flocculation in 37 per cent, elevated serum globulin in 35 per cent, low cholesterol esters in 21 per cent, and an elevated alkaline phosphatase in 17 per cent. There was often no correlation between clinical, biochemical, and histologic findings. The lack of correlation of biochemical tests and histology suggests the latter is not responsible for observed liver function changes (8)

Therapeutic Aspects

It is not possible to predict therapeutic responses from hepatic studies in congestive heart failure, although hepatic changes are rapidly altered with improvement of circulatory congestion in most patients. Hepatic tenderness, hepatomegaly, and splenomegaly disappear, the bromsulfalein, glycogen storage, prothrombin time, and cholesterol esters improve with cardiac compensation, abnormalities of serum protein, cephalin flocculation, thymol turbidity, and serum alkaline phosphatase often remain, however The usual therapeutic regimen including rest, digitalization, sodium restriction, and the use of diuretics is effective The following case history illustrates the influence of therapy on clinical, biochemical, and histologic changes in the liver in acute heart failure

Case 14 Effects of Treatment on Hepatic Abnormalities in Congestive Heart Failure

Clinical Features R E, a 36-year-old laborer, was hospitalized because of severe dyspnea associated with substernal pain Physical examination revealed rheumatic heart disease, an enlarged heart, regular sinus tachycardia, mitral stenosis and insufficiency, aortic stenosis and insufficiency Physical signs on admission included orthopnea, cyanosis neck vein distention, pulmonary congestion, and ankle edema The liver was palpable 6 cm below the right costal margin

The patient was given a regimen of bed rest a 500 mg sodium diet, mercurial diuretics, fluid ad libitum and digitalis Within 10 days all of the clinical and laboratory evidences of heart failure had disappeared

long-standing right sided heart failure. Central veins appear dilated and their walls are thickened. Similar changes are noted in hepatic veins and capillaries (5). Central necrosis is characterized by absence of cells in the centrilobular area (6). Fibrosis may be mild, moderate, or severe and is at first localized to the central area of the lobule. Moderate and severe fibrosis are accompanied by revascularization of the connective tissue stroma Rarely diffuse angiomatous changes (peliosis hepatitis) are encountered secondary to prolonged passive congestion.

Clinical Abnormalities

Clinical evaluation of 75 patients with congestive heart failure revealed hepatomegaly in 71 (95 per cent), jaundice in 16 (21 per cent), splenomegaly in 9 (12 per cent), and hepatic pain in 8 (11 per cent) The type of heart disease and duration of heart failure could not be correlated with signs and symptoms (2b). However, jaundice and hepatic pain were related to the severity and acuity of circulatory congestion An attempt has been made to explain the mechanism of encountered clinical abnormalities Icterus appears to be due to hepatocellular changes, although pulmonary infarction may be contributory. Ascites and peripheral edema are correlated with anatomic changes and the level of serum albumin Severe degrees of fibrosis and/or hypoalbuminemia are consistently accompanied by abnormal fluid retention Splenic congestion, embolization to the spleen, or thrombosis of the splenic vein may be responsible for splenomegaly in heart failure Hepatic pain and tenderness result from distention of the hepatic capsule by an engorged liver.

Biochemical Changes

Liver function tests are related to the severity of the heart failure (7). Serum protein alterations have been uniformly present in our studies. Poor carbohydrate storage occurred in 93 per cent of the patients studied, prothrombin deficiency in 90 per cent, abnormal bromsulfalein retention in 78 per cent, elevated serum

bilirubin in 40 per cent, a positive cephalin flocculation in 37 per cent, elevated serum globulin in 35 per cent, low cholesterol esters in 21 per cent, and an elevated alkaline phosphatase in 17 per cent There was often no correlation between clinical, biochemical, and histologic findings The lack of correlation of biochemical tests and histology suggests the latter is not responsible for observed liver function changes (8)

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The association of fluid retention and primary liver disease suggests that alterations in hepatic circulation (3), function (7), and histology (9) may contribute to chronic circulatory congestion. Nonhepatic factors such as renal dysfunction, infection, and marked cardiac impairment are often responsible for resistance to treatment Refractoriness may be attributed to hepatic abnormalities in 10–15 per cent of patients Treatment of hepatic changes which are secondary to passive congestion or poor nutrition requires special measures The functional and histologic changes in the liver furnish a basis for corrective therapy Improvement of cardiac function and maintenance of diuresis are both necessary. These patients may have two factors related to their liver dysfunction which the therapist can improve poor water tolerance and hypoalbuminemia. Restriction of fluid intake is desirable with a demonstrated water intolerance Infusion of salt-poor albumin may be helpful in selected patients with persistently low serum protein In most instances, correction of a serum albumin deficit will promote diuresis The antidiuresis accompanying its administration is its chief drawback However unless a significant serum albumin deficit is corrected, it is not possible to assign refractoriness to other causes

Patients with jaundice associated with congestive heart failure should be suspected of having centrilobular necrosis secondary to prolonged oxygen desaturation of blood in the hepatic venous system Careful search should be made for other mechanisms such as pulmonary infarction, viral hepatitis, or biliary obstruction which may be contributory It is desirable to employ a regimen of continuous oxygen and antibiotics in addition to usual therapeutic measures for congestive heart failure Special attention should be given to maintaining an adequate protein and vitamin intake

Heart Failure Secondary to Hepatic Disease

Circulatory congestion is responsible for hepatic dysfunction in most patients with a combination of heart failure and liver disease A common factor may cause cardiac and hepatic disability in patients with vitamin B complex deficiency, sub-

	Before therapy	After therapy
Biochemical study		
Serum bilirubin (mg %)	1 4	0 8
Bromsulfalein (%)	25	5
Alkaline phosphatase (B.U.)	2 2	5.2
Total serum cholesterol (mg %)	276	276
Cholesterol esters (mg %)	150	181
Serum albumin (Gm %)	3 9	3 8
Serum globulin (Gm %)	3 3	3 4
Cephalin flocculation	2+	1+
Thymol turbidity (units)	1 3	5 2
Glycogen storage (mg %)	4	25
Histologic study		
Fibrosis	0	0
Fat	0	0
Regeneration	1+	1+
Bile stasis	0	0
Inflammation	0	0
Necrosis	0	0
Other (congestion)	3+	0
Pathologic diagnosis	Passive congestion	Normal liver

Comment This case history demonstrates disappearance of all hepatic abnormalities with treatment of cardiac disability. The chief biochemical alteration was bromsulfalein retention, and this could be attributed to circulatory factors. Passive congestion was the only histologic alteration in the pretherapy biopsy.

Prognosis in general is related to the degree of liver disease in patients with necrosis or fibrosis on biopsy, and to the type of heart disease and severity of congestive failure in others (2b). The poorest response to treatment and the shortest survival period occur in patients with heart failure who exhibit clinical jaundice, hypoalbuminemia and/or central necrosis on biopsy. Patients with central necrosis and centrilobular fibrosis usually die in heart failure, hematemesis and hepatic coma are responsible for death in patients with diffuse fibrosis of the liver.

A major problem of therapy occurs in patients in congestive heart failure who have fluid retention refractory to treatment.

lar collapse are present in the terminal phases of hepatic vein thrombosis. Liver function tests show both excretory and metabolic functional abnormalities Hematologic study reveals a polycythemia, leukocytosis, anemia, or no abnormality depending on the etiologic mechanism.

Therapy is largely asymptomatic and supportive It should be

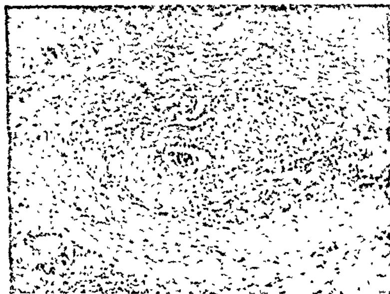


FIG 45 Periarteritis nodosum producing localized infarction of the liver

directed to causative factors Radioactive phosphorous, phlebotomy or spray irradiation are desirable in patients with polycythemia vera, antibiotics should be employed in the presence of an infectious process Supportive measures include analgesics, paracentesis, anticoagulants, parenteral fluids, oxygen, and vasoconstrictor agents

Hepatic Artery Occlusion

Hepatic artery occlusion has been noted in patients with *embolization in bacterial endocarditis or from mural thrombi in*

endocardial fibrosis, hemosiderosis, glycogen storage disease, amyloidosis, metastatic malignancy, or infectious diseases such as tuberculosis, syphilis, and parasitic infestations. In some instances, congestive failure appears to develop secondarily to hepatic insufficiency. This is principally seen in patients with hypervolemia associated with anemia and marked sodium retention, or following the administration of salt-poor albumin. Clinical studies show an elevated venous pressure, decreased circulation time, and an increased cardiac output (10). An occasional patient is observed in whom circulatory alterations incident to revascularization of the hepatic bed are the major cause of increased cardiac output Therapy consists of routine measures for hepatic disease, and correction of thiamine hydrochloride deficiency, anemia, and sodium retention which may contribute to circulatory congestion.

Hepatic Vein Thrombosis

Hepatic vein occlusion usually occurs as a complication of phlebitis, polycythemia, malignancy, or extension of a thrombus from the inferior vena cava. Case reports have described many other causes including granulomas, cysts, abscesses, leukemia, thrombotic thrombopenia, toxins, pregnancy, and chest trauma (11) One or all of the hepatic veins may be involved by occlusion. Morphologic alterations depend upon the amount of involvement Severe venous engorgement occurs as a result of interference with the exit of blood from the liver and leads to centrilobular necrosis This is followed by hemorrhage and inflammation during the acute phases. Fibrosis and liver cell regeneration are noted if healing occurs

Thrombosis of hepatic veins may be asymptomatic when onset is slow, but it is accompanied by marked symptoms when occlusion is sudden Symptoms are caused by backing up of blood in the liver Characteristically, there is some right upper quadrant pain due to a rapidly enlarging liver. The pain is often associated with shock, fever, and mild jaundice. Ascites is also conspicuous. The patient may deteriorate rapidly and succumb in one to four days. Hemorrhagic tendency, hepatic coma, and peripheral vascu-

is increased pressure in the portal vein. The congenital form of this disease is associated with atrophy or hypoplasia of the liver, in the acquired form, varying degrees of hepatomegaly may be present. Clinically, there is a venous murmur which varies in intensity and location It is often accompanied by a palpable thrill. Laboratory studies show findings characteristic of cirrhosis X-ray visualization of the patent vessel may be obtained by use of a radiopaque dye Treatment consists of supportive measures to improve general nutrition and to control bleeding tendency Marked esophageal varices are present Portacaval shunts eliminated venous hums and controlled portal hypertension in three patients with an acquired Cruveilhier-Baumgarten syndrome reported by Jahnke, Palmer, and Brick (15)

Acquired occlusion of the portal vein is seen in a variety of conditions (Fig 45c) It occurs most commonly as a spontaneous event in cirrhosis It is also seen as a complication of biliary tract disease, polycythemia, congestive heart failure, pancreatitis, peritonitis, and malignancy Occasionally the portal vein is ligated at the time of abdominal surgery Signs and symptoms depend upon the effect of the vascular occlusion on morphology of the liver. With sudden occlusion of the portal vein, there is usually severe abdominal pain, ascites, and gastrointestinal symptoms In most instances of slow occlusion recognizable symptoms are not present unless there is pre-existing closure of other vessels of the liver Ill effects have not been noted following experimental ligation of the portal vein in patients with metastatic malignancy (16) Therapy should be directed to the disease process which predisposes to portal vein occlusion Anticoagulants and antibiotics are sometimes indicated. Polycythemia should be treated with radioactive phosphorous or phlebotomy.

Aneurysm of the Hepatic Artery

Aneurysms may involve the common hepatic artery or any of its branches They vary in size from that of a pea to a cantelope and are usually saccular but may be fusiform They are caused by arteriosclerosis, syphilis, trauma, or congenital weakness and

the heart or aneurysms, periarteritis nodosa, thrombosis of hepatic arterial aneurysms, endarteritis of the hepatic artery, and neoplastic obstruction. Effects of the occlusion have been extensively studied *in patients receiving elective or accidental ligation of the hepatic artery at surgery.* Infarction of the liver may occur with complete interruption of hepatic arterial blood flow (12), the degree depending upon the site and cause of the occlusion, inherent capacity to develop collaterals, and the type of treatment. Typically, the infarcted area is yellowish, white (anemic), or red (hemorrhagic). In anemic infarcts, the sinusoids are empty, whereas in hemorrhagic infarcts, hemoglobin and its products are conspicuous. In both instances, necrosis involves the entire lobule although the architectural pattern of the liver is usually preserved. This contrasts sharply with the localized infarction seen with occlusion of smaller radicles of the hepatic artery (Fig. 45).

Acute occlusion of the hepatic artery is associated with fever, shock, jaundice, and evidence of renal failure. Biochemical study shows marked excretory and metabolic dysfunction. Treatment is usually unsatisfactory but should include antibiotics, supportive transfusions, oxygen, and parenteral fluids.

Portal Vein Occlusion

Partial or complete portal vein occlusion is the most frequent vascular abnormality encountered in liver disease (13). It may be congenital or acquired. Patients with congenital stricture of the portal vein are usually seen during early childhood because of symptoms incident to portal hypertension. There is frequently *enlargement of the spleen, prominent abdominal veins,* and esophageal varices. Massive hematemesis is often the presenting symptom. Portal decompression by a porta caval shunt is the therapy of choice.

The Cruveilhier–Baumgarten syndrome is characterized by a *patent umbilical vein, hypoplasia of the liver,* hepatic fibrosis, splenomegaly, and a caput medusa (14). During the normal course of development, umbilical veins atrophy to form the ligamentum teres within the falciform ligament. The umbilical veins may not close, but if they do, they sometime reopen when there

biopsy There may be low-grade impairment of excretory functional capacity. In contrast, it is difficult to differentiate clinical and biochemical abnormalities in hemolytic anemia from those seen in primary hepatic disease Needle biopsy is sometimes diagnostic in hemolytic disease since there is puddling of the red blood cells in the sinusoids, erythrophagocytosis by Kupffer cells, and various degrees of liver cell degeneration and inflammation These lesions are seen in sickle cell anemia (20) and acquired hemolytic anemia Sinusoidal obstruction and agglutinative thrombi of hepatic capillaries produced by sickle cells cause liver cell necrosis and may lead to localized or diffuse fibrosis of the liver Treatment consists of temporary control of the hemolytic process with adrenal steroids, correction of the anemia with fresh whole-blood transfusions, and supportive measures including oxygen, bed-rest, and antibiotics

Myeloid Metaplasia

Extramedullary hematopoiesis is often seen in liver biopsy sections from patients with bone marrow suppression (21) Of 105 patients with evidence of myeloid metaplasia on postmortem sections of the liver reviewed in our laboratory, 29 (27 per cent) had pneumonia, 22 (20 per cent) had malignant disease, 20 (19 per cent) had renal disease, 12 (11 per cent) had abdominal suppuration, 6 (5 per cent) had tuberculosis, and 17 (16 per cent) had miscellaneous infections The syndrome of myeloid metaplasia is characterized by splenomegaly, anemia, immature cells of the red and white series in the peripheral blood, a hyperplastic or deficient bone marrow and evidence of extramedullary hematopoiesis Myeloid metaplasia usually represents a compensatory phenomenon and should not influence specific therapy for the underlying process Its presence should not deter [illegible]

[illegible]

[illegible]

bone marrow, therefore, patients with myeloid metaplasia should be carefully followed-up for the appearance of splenic hyperactivity (21b)

may be intra- or extrahepatic. They are often associated with acute infections which aggravate the underlying disease.

The condition should be suspected when the combination of abdominal pain, gastrointestinal hemorrhage, and jaundice (17) is present. Abdominal pain is due to encroachment of the lesion on other structures. Hemorrhage results from erosion of the aneurysm into the biliary system, duodenum, or stomach. Jaundice is due to compression of common or hepatic ducts. The diagnosis is made by identifying a pulsating mass with a systolic bruit and confirmed by aortography (18). Biochemical liver function studies are normal unless there is biliary obstruction due to bile duct compression. Stools may show gross or occult blood with intestinal bleeding. An x-ray occasionally demonstrates calcification in the aneurysm. New technics in vascular surgery make it possible to treat these aneurysms successfully if the diagnosis is established while the patient is able to tolerate operative intervention. Ideal therapy consists of surgical resection with an end-to-end anastomosis, or use of a homologous graft.

Polycythemia Vera

Polycythemia is frequently associated with hepatomegaly and splenomegaly. It occasionally mimics hepatic cirrhosis with jaundice, fluid retention, and hepatosplenomegaly (19). *Plethora and* bleeding tendencies are characteristic. Hepatic abnormalities are usually due to thrombosis of the hepatic or portal vein. However, centrilobular necrosis may result from complicating congestive heart failure. *Biochemical liver function tests are markedly ab*normal with liver cell necrosis but are normal otherwise. Hematologic evaluation reveals polycythemia and a normal oxygen saturation. Histologic study reveals a normal, congested, or necrotic liver. *Treatment is that of the primary disease and consists of* phlebotomy, body irradiation, or use of radioactive phosphorus.

Anemia

Composite studies of the liver in iron deficiency anemia, pernicious anemia, and anemia due to primary bone marrow depression show few clinical alterations and a normal histology on needle

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Shock

The decrease in hepatic blood flow which occurs in shock produces hypoxia and if continued causes profound biochemical and morphologic changes. The normal balance of VEM and VDM is disturbed as excess VDM is produced and less is also inactivated by the liver (22). Increase in circulatory VDM contributes to the irreversibility of shock Cocarboxylase and cozymase enzyme systems become disorganized and are responsible for metabolic disturbances (23). Shock produces central necrosis when it persists for more than 24 hours. There is a disappearance of hepatic cells in the area around the central vein and the remaining sinusoids are filled with blood (24). Treatment consists of correcting etiologic factors, and providing supportive measures such as transfusions, vasopressor agents, oxygen, and antibiotics

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THE LIVER IN BILIARY OBSTRUCTION AND INFECTION

THE BILIARY system and parenchymal cells of the liver are interdependent. Disturbances in bile flow cause liver cell damage, and conversely injury of the parenchyma produces abnormalities in bile excretion. Biliary disease may be due to extrahepatic obstruction, an ascending biliary infection without obstruction, inflammation of the cholangioles, or a congenital abnormality. If the pathogenetic mechanism continues without interruption, all of these processes eventually lead to chronic liver disease.

Extrahepatic Biliary Obstruction

Extrahepatic biliary obstruction is most often due to a common duct stone or a pancreatic neoplasm. Other causes include bile duct carcinoma, cancer of the gallbladder, congenital atresia of the bile ducts, acquired stricture of the common bile duct, and compression of bile ducts by adhesions, metastatic carcinoma, granulomas, or lymphoblastoma. Serial needle biopsy of the liver has permitted reconstruction of pathologic events which occur during biliary obstruction (1). The duration of biliary obstruction and the occurrence of an ascending infection are important in determining the end results (Fig. 46).

The initial pathologic change in biliary obstruction consists of bile stasis with thrombi (Fig. 47 top left). This is followed in

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The initial pathologic change in biliary obstruction consists of bile stasis with thrombi (Fig. 47 top left). This is followed in

2–4 weeks by an inflammatory reaction in the portal area ᵖ consists of polymorphonuclear leukocytes, lymphocytes, mononuclear cells (Fig 47 top right). Continued obstructio period of 3–4 months produces biliary fibrosis with incre fibroblasts and collagen fibers in the portal area (Fig 47 b right) After 10–12 months, fibrosis is seen throughout the l and is accompanied by proliferation of bile ducts and no regeneration of liver cells (Fig. 47 bottom left). In the end st it is difficult to differentiate biliary fibrosis from connective t

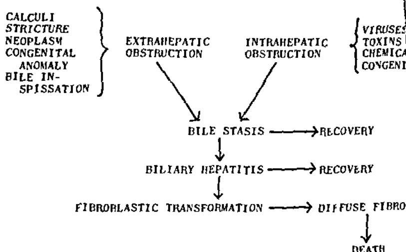
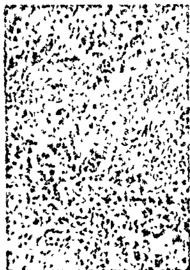


FIG 46. Evolution of chronic liver injury in biliary obstructon

changes due to other etiologic factors Liver cell regeneration less conspicuous and bile duct proliferation is more prominent biliary cirrhosis (2).

Clinical signs depend upon the stage of the process. Hepa megaly occurs in all phases although there is no correlation l tween the degree of liver enlargement and the duration or ca of obstruction. Jaundice is usually present except in patie with intermittent obstruction Hepatic tenderness and prurit are common Less frequently, patients exhibit splenomegaly, flu retention, and esophageal varices Hepatic pain is occasional marked in patients with biliary hepatitis, presumably due to combination of inflammation of the parenchyma and distenti



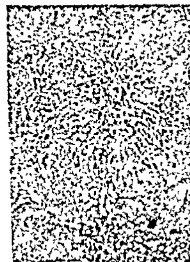



Fig. 47 The liver [illegible]

2–4 weeks by an inflammatory reaction in the portal area which consists of polymorphonuclear leukocytes, lymphocytes, and mononuclear cells (Fig. 47 top right) Continued obstruction for a period of 3–4 months produces biliary fibrosis with increase of fibroblasts and collagen fibers in the portal area (Fig. 47 bottom right) After 10–12 months, fibrosis is seen throughout the lobule and is accompanied by proliferation of bile ducts and nodular regeneration of liver cells (Fig 47 bottom left). In the end stages, it is difficult to differentiate biliary fibrosis from connective tissue

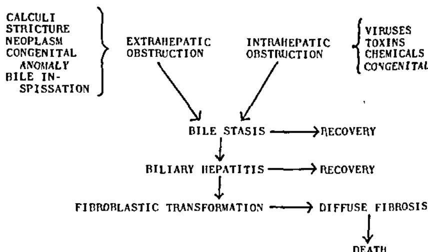


FIG 46. Evolution of chronic liver injury in biliary obstruction

changes due to other etiologic factors. Liver cell regeneration is less conspicuous and bile duct proliferation is more prominent in biliary cirrhosis (2)

Clinical signs depend upon the stage of the process Hepatomegaly occurs in all phases although there is no correlation between the degree of liver enlargement and the duration or cause of obstruction. Jaundice is usually present except in patients with intermittent obstruction. Hepatic tenderness and pruritus are common Less frequently, patients exhibit *splenomegaly, fluid retention,* and *esophageal varices* Hepatic pain is occasionally marked in patients with biliary hepatitis, presumably due to a combination of inflammation of the parenchyma and distention

of the liver capsule Pruritus occurs predominantly in the presence of high levels of serum bilirubin Splenomegaly is seen with both portal fibrosis and diffuse fibrosis and is occasionally accompanied by esophageal varices and other signs of portal hypertension Fluid accumulation is rarely a prominent finding Signs of portal hypertension are less prominent than in nutritional cirrhosis. This has been attributed to the fact there is less nodular regeneration of liver cells.

Biochemical tests show both excretory and metabolic functional changes (3) The serum alkaline phosphatase is the most valuable excretory test However, it is usually normal with intermittent obstruction Progressive elevation of the alkaline phosphatase

80 per cent of patients with calculous obstruction, 93 per cent of patients with obstruction due to neoplasm, atresia, and stricture, 75 per cent of patients with biliary hepatitis, 93 per cent with portal fibrosis, and 75 per cent with biliary cirrhosis Rise in total serum cholesterol parallels increase in alkaline phosphatase during the initial phases of obstruction It is less reliable as a test because of the variety of metabolic disturbances which can influence its results Tests of metabolic function including serum cholesterol esters, serum albumin and globulin, cephalin flocculation, and thymol turbidity are correlated with parenchymal cell changes to give accurate data for diagnosis Abnormalities in these tests are noted particularly in patients with prolonged obstruction or a complicating ascending infection

Diagnosing extrahepatic biliary obstruction may be difficult It is usually impossible to differentiate from the clinical, biochemical, and histologic abnormalities seen in cholangiolitic disease due to viral hepatitis, arsenicals, and nonobstructive bacterial cholangitis from extrahepatic obstruction Prolonged observation provides the answer Where there is complete uncertainty, surgical exploration is advisable

Where extrahepatic biliary obstruction requires surgery, it is desirable to know the nature of the lesion before operation Complete obstruction in the newborn or in patients with previous

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Biochemical tests show both excretory and metabolic functional changes (3) The serum alkaline phosphatase is the most valuable excretory test However, it is usually normal with intermittent obstruction Progressive elevation of the alkaline phosphatase occurs with complete biliary obstruction Bone growth and disease must be excluded if this test is used in the diagnosis of hepatobiliary disease In our studies, it was above 10 Bodansky units in 80 per cent of patients with calculous obstruction, 93 per cent of patients with obstruction due to neoplasm, atresia, and stricture, 75 per cent of patients with biliary hepatitis, 93 per cent with portal fibrosis, and 75 per cent with biliary cirrhosis Rise in total serum cholesterol parallels increase in alkaline phosphatase during the initial phases of obstruction It is less reliable as a test because of the variety of metabolic disturbances which can influence its results Tests of metabolic function including serum cholesterol esters, serum albumin and globulin, cephalin flocculation, and thymol turbidity are correlated with parenchymal cell changes to give accurate data for diagnosis Abnormalities in these tests are noted particularly in patients with prolonged obstruction or a complicating ascending infection

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Where extrahepatic biliary obstruction requires surgery, it is desirable to know the nature of the lesion before operation Complete obstruction in the newborn or in patients with previous

biliary tract surgery suggests congenital and acquired strictures, respectively. The diagnosis of congenital atresia can be made with certainty only by surgical exploration of the extrahepatic biliary system. A preoperative diagnosis of neoplasm is made on the basis of statistical probability, clinical features, x-ray changes, or exfoliative study. *Incomplete obstruction of bile outflow* and signs and symptoms of gallstones are also diagnostic of calculous disease.

The cause of extrahepatic biliary obstruction may be elusive at the time of exploratory surgery. The lesion is sometimes difficult for the surgeon to locate because of old adhesions which disturb anatomic relationships. If the gallbladder appears normal and the bile ducts are patent, it is necessary to consider the processes which produce intermittent obstruction. These include a tumor of the ampulla of Vater, intrahepatic stones, and a *junctional tumor* of the hepatic ducts. Cholangiography should be used (Fig. 48) to recognize common duct stones, exclude a lesion of the papillae or ampulla of Vater, and intrahepatic stones or tumor (4).

Treatment of extrahepatic biliary obstruction consists of early diagnosis and surgical intervention. Early surgery for repair of congenital atresia of the bile ducts and resection of neoplasms is essential. Parenchymal liver cell changes secondary to biliary obstruction increase operative morbidity and mortality and may eventually cause hepatic failure. An attempt should be made to improve hepatic functional capacity preoperatively. Operative preparations include: transfusions to return hemoglobin level to normal, glucose infusions to improve depleted glycogen stores; vitamin K to correct hypoprothrombinemia; and parenteral fluids and electrolytes to correct dehydration or ionic deficiencies.

Choice of an anesthetic depends upon the general condition of the patient, the anticipated procedure, and the preferences of the anesthetist and surgeon. In our experience, cyclopropane and local or regional block have been most satisfactory. However, patients with minor hepatic damage also tolerate spinal anesthesia, ether, and barbiturates well.

Morbidity and mortality following operative intervention are related to histology and biochemical patterns. Patients with an

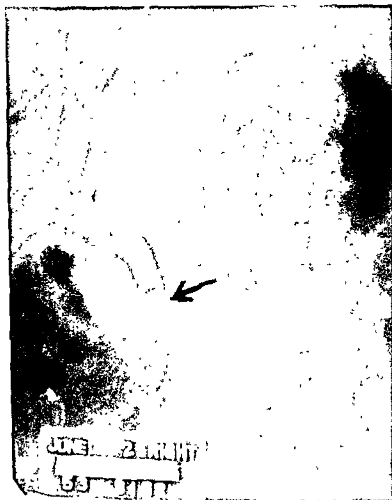


Fig 48 Cholangiogram showing common-duct stone

inflammatory hepatitis or mild fibrosis secondary to biliary obstruction usually have an uncomplicated postoperative course. Biliary cirrhosis is usually characterized by a progressive downhill course despite relief of obstruction. Postoperative biopsy may show shrinkage and pyknosis of fibroblastic nuclei and disappearance of inflammatory changes. The potential reversibility of clinical and laboratory alterations incident to biliary obstruction is illustrated by the following case history.

CASE 15 REVERSIBILITY OF CLINICAL, BIOCHEMICAL, AND HISTOLOGIC ALTERATIONS IN BILIARY OBSTRUCTION

Clinical Features M.W., a 74-year-old housewife, was hospitalized for recurrent right upper quadrant pain of six months duration. During the preceding six weeks, she had had chills and fever associated with pain radiating into her back. Past history revealed that the patient had a cholecystectomy 35 years previously.

A diagnosis of incomplete biliary obstruction was made on the basis of symptoms, signs, an elevated alkaline phosphatase, and periportal fibrosis. An exploratory operation was performed and a large stone removed from the juncture of a newly formed gall bladder (dilated cystic duct) and the common bile duct. One year later, re-examination revealed no significant clinical, biochemical or histologic abnormalities.

	Before surgery	*1 year later*
Hepatomegaly	6 cm	0
Splenomegaly	1 cm	0
Spider angiomas	0	0
Icterus	1+	0
Fluid retention	0	0
Hepatic fetor	0	0
Biochemical study		
Serum bilirubin (mg %)	2 0	0 3
Bromsulfalein (%)	19 5	0
Alkaline phosphatase (B U)	28	3 4
Total serum cholesterol (mg %)	291	283
Cholesterol esters (mg %)	181	158
Serum albumin (Gm %)	2 95	3 4
Cephalin flocculation	3+	Neg
Thymol turbidity (units)	1.0	2 0

	Before surgery	1 year later
Histologic study		
Fibrosis	2+	0
Fat	0	0
Regeneration	2+	1+
Bile stasis	0	0
Inflammation	2+	0
Necrosis	0	0
Other	Marked fibroblastic activity	0
Pathologic diagnosis	Biliary hepatitis with fibrosis	Normal liver

Congenital Atresia of the Extrahepatic Bile Ducts

Congenital atresia of the extrahepatic bile ducts is a special problem in itself This is a relatively infrequent anomaly which occurs once in approximately every 20–30 thousand births (5) An arrest in the development in the solid stage of embryogenesis is probably responsible for the anomaly Characteristically, jaundice occurs after birth and is associated with hepatomegaly, dark urine, light stools, and biochemical liver dysfunction It is desirable to operate within the first four or five weeks of life to prevent irreversible alterations in the liver The potential ability to correct biliary atresia can be determined only by surgical exploration A careful search for patent bile duct remnants is necessary Cholangioenterostomy or hepatojejunostomy have been proposed as surgical approaches in the treatment of complete extrahepatic biliary atresia The majority of patients with congenital atresia do not have lesions which are amenable to anastomosis of duct remnants to the gastrointestinal tract (5) However, this surgical procedure should be carried out whenever possible Anastomosis can be made between the hepatic duct, gallbladder or common duct, and the duodenum or jejunum. Unfortunately, most patients have severe hepatic damage at the time of surgery and although adequate reconstructive surgery is performed, progressive hepatic insufficiency continues



FIG 49 Gastrointestinal series showing a wide duodenal sweep in adenocarcinoma of the head of the pancreas

Carcinoma of Ampulla of Vater and Head of Pancreas

One to two per cent of all malignant tumors are in the region of the ampulla of Vater and head of the pancreas (6) The lesion is most common in the age group of 40–70 years, but may occur in the early twenties. Carcinoma of the head of the pancreas consists of adenocarcinoma of duct cell or acinar origin Mucocystadenocarcinomas and islet cell carcinomas are infrequent Ampullary carcinomas are usually papillary or malignant carcinoids.

The diagnosis of neoplastic biliary obstruction should be entertained with the onset of jaundice in any patient over 40 years of age. Anorexia, nausea, vomiting, diarrhea, and constipation are common symptoms. Jaundice occurs earlier in ampullary carcinoma than with pancreatic head tumors It is frequently accompanied by pruritus Dull epigastric pain which radiates to the back and is relieved by sitting or stooping develops in some patients with pancreatic malignancy Abdominal pain is often colicky in ampullary tumors Both conditions are associated with weight loss However, it is more marked in pancreatic cancer (7)

Physical examination shows a distended gallbladder in approximately 30 per cent of patients with neoplastic obstruction to bile outflow Evidence of complete obstruction is revealed in biochemical liver function studies There is an elevated direct serum bilirubin, biliuria, and no urine or fecal urobilinogen The serum alkaline phosphatase and total serum cholesterol are increased and unless there is a complicating infection, cholesterol esters, flocculation tests, and protein patterns are usually normal The carcinoma is sometimes revealed by radiologic study A widened duodenal sweep is noted with pancreatic head carcinoma (Fig. 49), and enlargement of the papilla of Vater or malignant ulceration of the second portion of the duodenum occurs in ampulla of Vater neoplasms (Fig 50) A positive diagnosis may be established preoperatively by obtaining exfoliative cell studies (8) Duodenal contents are obtained by intubation, using either a Levine or a Rehfuss tube The tube should not be lubricated



Fig 50 Malignancy of the second portion of the duodenum producing obstructive jaundice

Fluoroscopy is useful in determining the location of the tip of the tube as it is inserted Specimens of fasting gastric juice and *bile are collected separately in receptacles chilled in an ice bath* The fluid is promptly neutralized to *p*H 7 and centrifuged at 1800 revolutions per minute for 10 minutes Smears of the moist sediment are fixed and staining is then carried out using the method described by Papanicolaou.

Therapy of choice in both carcinomas consists of pancreaticoduodenal resection (9) Prognosis is poor in pancreatic cancer despite radical surgery, and few patients with this disease survive as long as five years Survival is increased from a baseline of one to two months in patients receiving exploratory laparotomies as the only procedure, to five to nine months where palliative *decompression operations are performed* The average survival time following pancreatoduodenal resection is seven to eleven months (10) Palliative surgery provides considerable help by relieving pruritus and improving general nutrition A surgical procedure whereby the biliary tract is anastomosed to the digestive tract is recommended Cholecystojejunostomy is desirable when feasible Cholecystogastrostomy, cholecystoduodenostomy, and simple cholecystostomy are indicated in individual cases

Ampulla of Vater lesions present a more encouraging outlook Radical pancreaticoduodenal resection or transduodenal local excision may be curative In severely ill patients, a two stage procedure is desirable The remaining tail of the pancreas does not present a problem for it may be anastomosed to the gut or the ducts ligated and the cut end oversewn (7)

COMMON DUCT STONES

Common duct stones constitute the most frequent cause of biliary *obstruction In a series of 103 consecutive patients with* extrahepatic obstruction in the Jersey City Medical Center, 53 had calculous disease A correct preoperative diagnosis was made on basis of the symptom complex in 83 per cent of the cases Common duct stones occur in association with cholecystitis without jaundice, they may also be found at the time of gallbladder surgery. Their symptom complex is variable Pain is present in over 90

per cent of patients (11) and it is frequently located in the epigastrium with radiation into the back. Anorexia, nausea, and vomiting are the next most prominent symptoms, occurring in 85 per cent of patients Chills and fever are noted in 40 per cent.

Common duct stones should be suspected where there is a history of recurrent jaundice, biliary colic, and dyspepsia An abdominal x-ray may reveal a characteristic radiopaque shadow. With jaundice, serial quantitative studies of urine bile and urobilinogen are invaluable. The direct serum bilirubin is elevated and the urine often contains both bile and urobilinogen because of incompleteness of obstruction. The serum alkaline phosphatase and total serum cholesterol may be elevated. Cholesterol esters, flocculation tests, and other measures of metabolic function are normal Gallbladder x-rays are not helpful with jaundice due to biliary obstruction They may be useful indirectly, however, where a patient is suspected of having viral hepatitis and the serum bilirubin is less than 11 mg/100 cc After subsidence of jaundice, a gallbladder series or cholangiogram may be of diagnostic value

At surgery, dilatation of the common duct is present in approximately 80 per cent of patients, and there is associated chronic pancreatitis in 30 per cent (12) A stone can be palpated in 25 per cent. Indications for common duct exploration in the absence of a palpable stone include a dilated duct, small stones in the gallbladder, and enlargement or thickening of the head of the pancreas Exploration is also indicated when another cause for icterus cannot be found Cholangiography is a valuable diagnostic adjunct when direct visualization does not provide a definite answer (4).

Therapy consists of removal of the common duct stone It is essential to avoid injury to the ducts in both exploration and removal of impacted stones Jaundice may occur after removal of a gallbladder and common duct stones due to the presence of intrahepatic stones or the formation of cystic duct stones

A major problem is presented by the patient with an ascending cholangitis and a common duct stone A localized abscess or miliary abscesses occur as a complication It is necessary to treat

sepsis and undertake relief of biliary obstruction as soon as feasible These patients are usually hospitalized with jaundice, chills, fever, and evidence of malnutrition There is an anemia with a leukocytosis, and x-rays of the chest often show marked elevation of the diaphragm Blood cultures are frequently positive for *Esch coli* and other enteric organisms A combination of tetracycline derivatives, Streptomycin penicillin, and whole-blood transfusions improves the general physical state and permits operative intervention

Primary Cholangiolar Disease

Intrahepatic diseases sometimes involve the cholangioles and produce clinical, biochemical, and histologic changes similar to those of extrahepatic biliary obstruction The concept of primary cholangiolar injury has been presented from several different points of view in earlier sections of this monograph The following discussion will consist of a brief general review of current concepts of its etiology, pathology, mechanism of encountered clinical features, diagnostic criteria, and treatment

The virus of hepatitis appears to be the most common etiologic agent in cholangiolar disease (13) *Str viridans* infections (14), toxins, and drugs such as chlorpromazine (15), arsenicals (16), and methyl testosterone (17) produce a similar pathologic state Atresia of the intrahepatic bile ducts is infrequently responsible (18). In many instances, the disease is insidious in its onset and it is not possible to establish its cause

Serial liver biopsies demonstrate stages in transition of cholangiolitic hepatitis to cholangiolitic cirrhosis in patients who do not respond to therapy Initial biopsy shows bile stasis with bile thrombi located in many of the cholangioles Subsequently, there is swelling of the cholangioles and a pericholangiolitis is prominent Fibrosis of the liver is noted after a period of several months (19)

Interruption of bile outflow has been attributed to mechanical obstruction of the cholangioles as a result of bile thrombi and pressure from swollen liver cells Neither of these postulates seems to be tenable. Watson and Hoffbauer feel that leakage or dia-

pedesis of the bile results from *increased permeability of the* cholangioles (13) According to this theory, bile constituents which enter the bile capillaries are regurgitated into the blood stream. An alternative hypothesis is that regurgitation of the *bile is due to the excretion of liver cells directly into the lymph* spaces of Desse.

Pruritus is the most common symptom in cholangiolar disease and is presumably due to the return of bile acids and salts or other constituents of bile to the blood. Jaundice, hepatomegaly, and splenomegaly are prominent in the subacute and chronic stages. Varying degrees of hepatic insufficiency including fluid retention, spider angiomas, and esophageal varices may be present. Xanthomatosis is prominent in patients with pronounced elevation of the serum lipids.

Biochemical study shows a pattern identical to that seen in *complete extrahepatic biliary obstruction. There is an elevated* "one minute" bilirubin, increased serum alkaline phosphatase, and hypercholesterolemia Metabolic function tests are within normal limits Differentiation from extrahepatic biliary obstruction requires exploratory surgery with cholangiography, except in patients who have rapid spontaneous subsidence of cholangiolitic hepatitis.

Treatment consists of rest, diet, and corticotropin or adrenal steroids These drugs should be given in therapeutic amounts until there has been complete disappearance of jaundice. Prognosis improves with adrenal steroid therapy Serial biopsies show a suppression of inflammatory reactions and fibroplasia following adequate treatment in most instances Occasionally the disease progresses despite the use of steroids, antibiotics, and other available measures, and eventually leads to cholangiolitic cirrhosis. (See Case History 11.)

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1

NEOPLASTIC DISEASE OF THE LIVER AND LIVER TRAUMA

NEOPLASTIC DISEASE

THE LIVER is a frequent site of neoplastic disease. It is often involved in metastatic carcinoma and may harbor primary malignant or benign tumors. Recognition of metastatic carcinoma of the liver is of paramount importance for proper therapeutic and prognostic perspective in patients with neoplastic disease. Current methods of detecting liver metastases include clinical evaluation, biochemical tests, portal venography, radioisotope localization technics, and needle biopsy of the liver. Hepatosplenography by Thoratrast is helpful in detecting late metastases but the usefulness of this procedure is limited because of its carcinogenic potential. These methods are also helpful in recognizing primary malignant lesions of the liver which are superimposed on chronic hepatic disease.

Metastatic Malignancy of the Liver

The normal liver provides a good medium for cancer cell multiplication (1). Incidence of hepatic metastases varies depending on the site and extent of the primary neoplasm. A study at the Jersey City Medical Center showed a high percentage of hepatic metastases in patients dying from primary lesions of the

Table 17. Metastatic Disease of the Liver
Routine Autopsy Study, the Jersey City Medical Center (1947-1951)

Primary Neoplasm	*Total*	*With hepatic metastases* *No*	*%*
Gallbladder	2	2	100 0
Pancreas	43	34	79 0
Adrenal	5	3	60 0
Parotid gland	2	1	50 0
Testes	2	1	50 0
Colon	90	43	47 7
Kidney	24	11	45 8
Rectum	42	18	42 8
Stomach	80	34	42 5
Breast	41	16	39 0
Bile duct	12	4	33 3
Melanoma	3	1	33 3
Thyroid	3	1	33 3
Bronchogenic	108	30	27 7
Larynx	9	2	25 0
Pharynx	8	2	25 0
Lymph glands	19	4	21 0
Urinary bladder	24	5	20 8
Ovaries	10	6	20 0
Uterus	34	5	14 7
Esophagus	44	6	13 6
Mouth	11	1	9 0
Small intestine	11	1	9 0
Prostate	46	4	8 7
Bone	3	0	0 0
Central nervous system	25	0	0 0
Lip	1	0	0 0
Skin	20	0	0 0
Tongue	10	0	0 0
Tonsil	3	0	0 0
Trachea	3	0	0 0

gastrointestinal tract, kidney, breast, and lung (Table 17) Metastases to a cirrhotic liver are less frequent because of the disturbed oxygen and blood supply and the poor nutritional status of the parenchymal cells Physical examination often reveals signs of the primary growth, or evidence of metastases to organs other than the liver Hepatic involvement may be reflected by enlargement or nodularity of the liver, jaundice, or ascites Rarely,

splenomegaly and spider angiomas are present. Signs and symptoms are of little value in detecting early metastatic cancer of the liver. Although clinical evaluation permits recognition of hepatic metastases in advanced phases of cancer, laboratory aids are necessary to differentiate early metastatic cancer from primary liver disease.

Biochemical studies also have a limited value in the early phase and are usually normal until the late phase. Their chief value is in establishing the general status of the patient since metabolic abnormalities incident to the neoplastic process may be reflected in their results.

Biochemical studies of 50 patients with histologically proven hepatic metastases in the Jersey City Medical Center revealed abnormal protein patterns in all, bromsulfalein retention in 70 per cent, elevated serum alkaline phosphatase in 60 per cent, positive cephalin flocculation in 47 per cent, and cholesterol ester disturbances in 47 per cent. The source of the primary neoplasm, its character and extent, and the nutritional status of the patient all seemed to influence the incidence and severity of biochemical abnormalities. A study of cancer without hepatic metastases also revealed a high incidence of abnormal liver function tests.

Neoplasms of the gastrointestinal tract are characterized by marked alterations in the protein patterns, due partly to malnutrition. The presence of anemia, infection, negative nitrogen balance, and other complications of malignancy are reflected in biochemical liver function tests. The degree of anaplasia of the neoplasm, and the occurrence of other morphologic lesions are important determinants of the biochemical patterns. Rapidly growing neoplasms are accompanied by a higher incidence of bromsulfalein retention, elevated serum alkaline phosphatase, positive flocculation tests, and abnormal enzyme studies. Hyperbilirubinemia is accompanied by an elevation of serum alkaline phosphatase and bromsulfalein retention. However, increased alkaline phosphatase is at times present without significant alteration of serum bilirubin, serum cholesterol, or bromsulfalein excretion (2). Excretory abnormalities are not correlated with

metabolic function studies such as protein partition changes, flocculation tests, cholesterol ester levels, or transaminase activity. Serial studies show an increase in the degree of functional alterations with progression of metastases and a decrease with control of the neoplastic process in the liver with surgery, chemotherapy, or radiotherapy.

It is desirable to obtain morphologic evidence of metastatic neoplasia whenever possible. Blind needle biopsy of the liver has been successful in 80–90 per cent of our patients with hepatomegaly where a nodule was palpable or resistance of neoplastic tissue felt with an exploring needle. Punch biopsy is of little help in patients without enlargement of the liver and it is necessary to employ the intercostal technic. Abdominal radioactive iodinated albumin surveys as described in Chapter Three may be valuable for such patients (3). Neoplastic lesions, more than 2 cm in diameter, cause abnormal localization of the iodinated albumin as a result of mechanical stasis or increased afinity of the cancerous tissue for iodine or albumin. An increase of more than 30 per cent above established normal values for radioactivity is suggestive of metastatic malignancy and provides a site for biopsy. Biopsies in an area not demonstrating localization of radioactive iodionated albumin are often normal, whereas, biopsy over "hot spots" provides neoplastic tissue in a high percentage of patients. False localization may occur in patients with diffuse parenchymal disease or granulomatous invasion of the liver. A major limitation of this combined approach is the fact that deep metastases are not accessible to biopsy. Where tracer studies indicate metastatic disease and biopsy is negative, surgical exploration is necessary to validate its presence and determine the extent of involvement.

The character of a metastatic lesion occasionally permits identification of the primary neoplasm when its source is not evident. Metastases are well differentiated or display varying degrees of anaplasia (Fig. 51a). The tissue in the area surrounding neoplastic cells often shows fibrosis, necrosis, inflammation, or fatty changes. Fibrotic reactions are sometimes so marked that it is not possible to positively identify cancerous areas in microscopic sections.

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Fig 51 *Neoplastic involvement of the liver,* A, *metastatic* adenocarcinoma from the stomach, B, leukemic infiltration (chronic lymphocytic); C, primary liver cell cancer (hepatoma), D, cholangioma

THERAPY

The introduction of new methods for early diagnosis and new surgical technics permits more effective treatment Operative removal of a single metastasis offers the best chance for control at the present time The occasionally successful resection of a solitary metastatic malignant lesion of the liver (4) makes it necessary to evaluate carefully each patient for possible surgical therapy, for there are patients who will not benefit from surgery

Hormonal therapy is valuable for patients with hepatic metastases from prostate, breast, ovarian, or adrenal cortex malignancy. Prostatic carcinoma often responds temporarily to estrogens and orchidectomy (5), and growth of breast cancer may be inhibited by androgens or estrogens (6) Adrenal steroids, bilateral adrenalectomy (7), or hypophysectomy (8) are helpful in selected patients with hormone dependent malignancy

Chemotherapy is indicated for liver invasion in Hodgkin's disease, lymphosarcoma, and leukemia (Fig 51b) Cytotoxic agents such as nitrogen mustards (9), and triethylene melamine (10) may cause regression of hepatomegaly, jaundice, and fluid retention in Hodgkin's disease and chronic leukemia Nitrogen mustards are given intravenously in two to four equal doses on consecutive days until a total of 0 4 mg Kg of body weight has been administered The course may be repeated when bone marrow function has recovered as determined by peripheral blood studies Barbiturates or chlorpromazine should be given before each injection of mustards to prevent nausea and vomiting Triethylene melamine is the preparation of choice where oral therapy can be tolerated since it produces fewer side effects A total dose of 10–15 mg given in divided doses over a two to six day period is usually satisfactory

Patients with jaundice or severe abdominal pain due to hepatic invasion of a radiosensitive neoplasm may benefit from x-ray therapy We have noted symptomatic relief in several patients who have received x-ray therapy as a palliative measure Supervoltage roentgen therapy has led to relief of gastrointestinal disturbances, gain of weight, improvement in liver function,

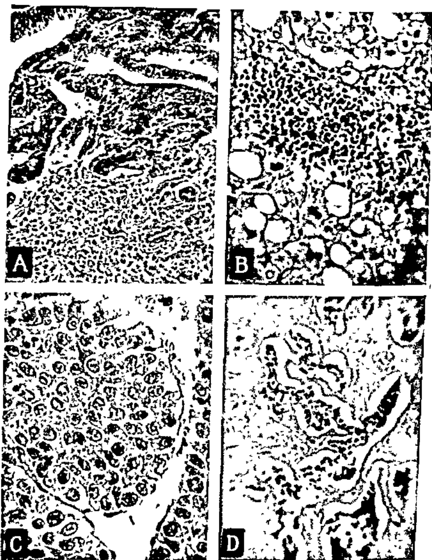


Fig 51 Neoplastic involvement of the liver, A, metastatic adenocarcinoma from the stomach, B, leukemic infiltration (chronic lymphocytic), C, primary liver cell cancer (hepatoma), D, cholangioma

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and necrosis of metastatic lesions (11). Radioresistant tumors are not affected by x-ray therapy The parenchyma of the liver is relatively insensitive to the effects of radiation, but marked systemic symptoms may occur following radiotherapy even when supervoltage technics are employed. Nitrogen mustard or one of its derivatives given before irradiation reduces the discomfort attributed to intracellular edema which follows radiotherapy. A total dose of 2000–3750 r. given through opposed anterior and posterior fields is usually adequate.

Primary Cancer of the Liver

We have observed 15 patients with primary liver cell cancer and 8 patients with bile duct cancer in our clinic during the past eight years. Cancer of the liver is more common in the colored races, predominates in males, and is usually seen between the ages of 50 and 65, although it may be encountered in infancy. A variety of chemical agents cause hepatic neoplasms in experimental animals, but no relationship to toxic agents has been demonstrated in man. Liver cell cancer is more frequent in patients who have chronic liver disease Nutritional cirrhosis was present in 12 (80 per cent) of our patients, and it has been reported as a complication of hemochromatosis (12), viral hepatitis (13), and chronic parasitic infections (14). Serial studies of patients with marked adenomatous hyperplasia show a transition to malignancy There appears to be a uniform gradation between regenerative hyperplasia and liver cancer.

Clinical recognition of primary liver malignancy is difficult because of a lack of specific symptoms Malignancy should be suspected whenever there is a rapid downhill course, or progressive hepatomegaly in a patient with hepatic cirrhosis The first evidence may be severe abdominal pain, fever, or symptoms and signs of metastases. Hematemesis, due to rupture of esophageal varices, was the principal symptom in four of our patients In one instance, shock incident to intra-abdominal hemorrhage was the dominant clinical feature. An enlarged, tender, irregular liver is the most frequent physical sign. Jaundice, ascites, and peripheral edema are sometimes present Physical

examination or radiologic studies may demonstrate elevation and decreased motion of the right diaphragm

Excretory and metabolic functional patterns usually reflect the status of underlying hepatic disease unless malignancy encroaches on major bile channels, or undergoes necrosis Liver biopsy may not be helpful in diagnosis for neoplastic areas are missed or interpreted as representing regenerative phenomena or metastatic cancer. In primary liver cell cancer, multinucleated tumor cells maintain a cord-like pattern surrounded by a capillary network (Fig. 51c), and in bile duct carcinoma typical tubules of cuboidal cells which often contain bile are present (Fig 51d) (15). The following case history illustrates the development of primary liver cell cancer in a patient with nutritional cirrhosis Serial clinical and biochemical studies were not diagnostic

Case 16 Primary Liver Cell Cancer

Clinical Features S T, a 55-year-old bartender, was hospitalized in March 1948 because of a cough and chest pain History revealed a prolonged poor dietary intake associated with alcoholism Examination showed an enlarged liver, and needle biopsy demonstrated evidence of moderate cirrhosis Following discharge, the patient continued to eat poorly and consume large quantities of whiskey He was readmitted in 1951 and 1952 because of hematemesis After bleeding was controlled by balloon tamponage in 1952, elective ligation of the hepatic and splenic arteries was performed Postoperatively, he developed fever, shock, and jaundice Postmortem examination revealed primary liver cell cancer, nutritional cirrhosis, infarction of the liver, and ruptured esophageal varices

	1948	*1949*	*1950*	*1951*	*1952*
Hepatomegaly	6 cm		6 cm		8 cm
Splenomegaly	2 cm		2 cm		2 cm
Spider angiomas	2+		2+		2+
Jaundice	0		0		0
Hepatic fetor	0		0		0
Ascites	0		3+		2+
Ankle edema	0		2+		2+
Bleeding esophageal varices	0		2+		4+
Hepatic coma	0		0		0

	1948	*1949*	*1950*	*1951*	*1952*
Biochemical study					
Serum bilirubin (mg %)	0.3	0	0	0	0.9
Bromsulfalein retention (%)	*Neg*	*0.5*	*20.5*	*10.5*	*10.5*
Serum alkaline phosphatase (B U)	..	.	..	2.4	4.7
Total serum cholesterol (mg %)	*276*	*171*	*182*	*104*	*128*
Cholesterol esters (mg %)	130	74	99	74	74
Serum albumin (Gm %)	3.1	3.6	3.6	2.9	3.0
Serum globulin (Gm %)	2.7	3.6	3.2	3.3	3.2
Cephalin flocculation	2+	3+	1+	4+	3+
Thymol turbidity (units)	1.5	1.0	3.0	1.0	0.5
Histologic study					
Fibrosis	3+	.	.	.	3+
Fat	*1+*	.	..	..	*0*
Regeneration	3+	.	.	.	3+
Bile stasis	0	..	.	.	0
Inflammation	2+		.	..	2+
Necrosis	*0*	.	..	..	*4+*
Other	0	..		..	Primary liver cell cancer
Pathologic diagnosis	Moderate nutritional cirrhosis				Moderate nutritional cirrhosis

Surgical removal of the primary malignancy is desirable wherever possible. The surgical status of the tumor can only be judged by laparotomy Marked replacement of hepatic parenchyma by tumor prior to appearance of clinical signs and symptoms prevents curative surgery in most instances (16). Small tumors near the margin of the liver may be excised by wedge resection Large or deep tumors confined to one lobe which do not involve major blood vessels or ducts are removable by hepatolobectomy (17). Pre-existing hepatic damage increases the surgical risk. The principal immediate complication of surgery has been hemorrhage Hypothermia (18), use of cautery and coagulating agents, and improved suture material have virtually eliminated this problem

In wedge resection, arteries, veins, and bile ducts are clamped

bectomy is carried out by isolating and ligating the left branch of the portal vein, hepatic artery, common bile duct, and hepatic vein through a vertical incision just to the left of the falciform ligament (4) Right hepatolobectomy is more difficult for one must preserve venous outflow from the left lobe, ligate the hepatic artery, and control bile drainage Right lobectomy is performed through a right thoraco-abdominal incision The round and triangular ligaments of the liver are separated and the liver retracted upward into the thorax The cystic duct, cystic artery, and right branches of the hepatic artery, hepatic duct, and hepatic veins are transected The base of the right lobe of the liver is then cut and the raw surface covered with falciform ligament (17)

Successful removal of primary liver cell and duct cell cancer has been achieved in a few instances (16) Neither nitrogen mustard nor x-ray therapy has been helpful in primary malignancy of the liver They often precipitate gastrointestinal reactions which add to the discomfort of the patient Nitrogen mustard and its derivatives have been introduced directly into the hepatic artery at laparotomy without improvement of end results

Cystic Diseases of the Liver

Nonparasitic cystic disease of the liver occurs as a part of congenital polycystic disease, a neoplasm, or an inflammatory process (19) Developmental defects are responsible for embryonal cysts, lymphatic cysts, and blood vessel cysts Bile duct obstruction causes retention cysts Pseudocysts consist of neoplasms that undergo necrosis or inflammation with softening and evacuation of their cortical portion

Cystic disease of the liver is usually asymptomatic Occasionally there is anorexia or dull epigastric pain Patients may have severe pain due to hemorrhage within the cysts, or twisting of the pedicle of the cyst Rarely, fever due to secondary infection

	1948	1949	1950	1951	1952
Biochemical study					
Serum bilirubin (mg %)	0.3	0	0	0	0.9
Bromsulfalein retention (%)	Neg	0.5	20.5	10.5	10.5
Serum alkaline phosphatase (B U)	..	..	..	2.4	4.7
Total serum cholesterol (mg.%)	276	171	182	101	128
Cholesterol esters (mg %)	130	74	99	74	74
Serum albumin (Gm %)	3.1	3.6	3.6	2.9	3.0
Serum globulin (Gm %)	2.7	3.6	3.2	3.3	3.2
Cephalin flocculation	2+	3+	1+	4+	3+
Thymol turbidity (units)	1.5	1.0	3.0	1.0	0.5
Histologic study					
Fibrosis	3+	..	..	..	3+
Fat	1+	..	..	..	0
Regeneration	3+	..	..	..	3+
Bile stasis	0	..	..	..	0
Inflammation	2+	..	..	..	2+
Necrosis	0	..	..	..	4+
Other	0	..	..	..	Primary liver cell cancer
Pathologic diagnosis	Moderate nutritional cirrhosis				Moderate nutritional cirrhosis

Surgical removal of the primary malignancy is desirable wherever possible The surgical status of the tumor can only be judged by laparotomy Marked replacement of hepatic parenchyma by tumor prior to appearance of clinical signs and symptoms prevents curative surgery in most instances (16) Small tumors near the margin of the liver may be excised by wedge resection Large or deep tumors confined to one lobe which do not involve major blood vessels or ducts are removable by hepatolobectomy (17) Pre-existing hepatic damage increases the surgical risk The principal immediate complication of surgery has been hemorrhage. Hypothermia (18), use of cautery and coagulating agents, and improved suture material have virtually eliminated this problem

permitted a preoperative diagnosis of hemangioma which was confirmed at the time of surgery Surgery is indicated as soon as the diagnosis is made to prevent spontaneous rupture, hemorrhage, and necrosis Hepatic lobectomy is the procedure of choice in some infants and adults (20)

LIVER TRAUMA

The liver is vulnerable to both direct and indirect trauma because of its size and superficial position Penetrating missiles are chiefly responsible for direct trauma, the degree of injury depending on their size, velocity, nature, and explosive effect Complications depend on the extent of hepatic damage Blood vessels and bile ducts are frequently torn and this causes secondary devitalization and necrosis of the liver parenchyma Tissue involvement extends beyond the pathway of the projectile. This results in profound clinical manifestations which include shock, signs and symptoms of blood loss, bile peritonitis, empyema, and renal failure

Recognition of rupture of the liver in the absence of a penetrating wound is sometimes difficult This type of injury commonly occurs in motor vehicle accidents Rupture may be subcapsular, central, or both The right lobe of the liver being larger and less protected, is injured more often than the left lobe There is a tendency for the organ to split in a stellate manner Symptoms of liver rupture may be delayed and include manifestations of hemorrhage and shock, and abdominal pain which is aggravated by motion or deep breathing Rarely, a tender, enlarged liver is felt Liver function tests are not helpful X-rays may show an elevated right diaphragm Peritoneoscopy and an abdominal tap, using a spinal needle, may be helpful, however, surgical exploration is more desirable (21)

Central or subcapsular rupture of the liver often causes hemorrhage into the bile ducts A cavity develops within the substance of the liver and collects bile and blood until sufficient pressure is developed to expel blood through bile ducts Blood clots block the bile ducts and cause pain or jaundice Traumatic hemobilia occurs several days after abdominal injury The diagno-

or gastrointestinal hemorrhage is the presenting symptom Physical examination shows an enlarged, nontender liver which feels cystic Biochemical liver function tests are not helpful. Needle biopsy of the liver may be diagnostic. Treatment consists of excision if the cyst is pedunculated. Enucleation, wedge resection, marsupialization, or drainage should be used if the cyst has a wide attachment (19)

Hamartoma

Hamartoma or mixed adenoma of the liver arises from fetal rests and is seen in infants and young adults. The tumor is usually solitary and consists of normal liver cords accompanied by distortion of the lobular pattern due to proliferation of connective tissue and bile ducts Symptoms are due to effects of mechanical pressure from the neoplasm. Examination reveals a mass which is firm and nontender Biochemical studies are normal in most instances Surgical intervention is the treatment of choice although it is usually not curative

Hemangioma

Hemangiomas are commonly found in the liver and rarely produce symptoms They represent a developmental anomaly and consist of hyperplasia of vascular elements to produce a capillary or cavernous type of overgrowth. Patients may complain of abdominal pain, distention, or nausea and vomiting. Physical examination often reveals an enlarged liver which may have a bruit Jaundice is sometimes present due to pressure on hilar structures. Biochemical liver function tests are normal in the majority of patients

Histology shows atrophic liver cells which are supported by a fibrous stroma and surround numerous blood spaces lined with a single layer of endothelium. Clinical diagnosis is difficult and is not made unless liver biopsy or surgical exploration is undertaken Needle biopsy is dangerous and should not be performed if the technic outlined in Chapter Four is followed From one of our patients pure blood was aspirated on three occasions with the #20 needle used for local anesthesia. This

injury of associated viscera, or represent overgrowth of the normal bacteria in the liver as a result of tissue alterations caused by blood loss and shock Antibiotics are essential to combat these infections which develop in areas of devitalized hepatic parenchyma Surgical therapy should be directed to the control of hemorrhage, establishing adequate bile drainage, debridement of devitalized and detached liver parenchyma, and evacuation of blood, blood clots, foreign bodies, and other debris An abdominal approach, using a vertical or transverse incision, may suffice A thoracic or combined thoracico-abdominal approach is preferable in patients with associated chest injury or persistent hemorrhage from a wound of the dome of the liver (21)

Hepatic sutures should be used only in superficial lacerations for in deep wounds they may cause liver cell necrosis or produce a closed cavity which contains blood, bile, or pus A slender, curved needle should be used for sewing Either cotton or catgut may be used Multiple drains are desirable to express bile and blood Absorbable and gauze packing or autographs such as omentum, muscle or peritoneum are sometimes required to control hemorrhage, although these agents increase morbidity and mortality if used routinely (23) Packs should be avoided if possible They retard healing because of their delayed absorption, and predispose to infection and necrosis by blocking drainage of bile, blood, and exudates Complications of this form of therapy include abscess formation, secondary hemorrhage, common duct stricture, biliary fistula, and intestinal obstruction Pain and hemorrhage often occur with the removal of a large liver pack

As emphasized by Madding (24), establishment of early adequate external drainage to allow escape of bile, blood, pus, and devitalized tissue is the most important part of therapy in liver trauma Most wounds require drainage In superficial liver wounds, the wide end of a Penrose cigarette drain is adequate Multiple drains should be placed within the liver substance and into the subhepatic and subphrenic spaces in patients with moderate to large hepatic wounds Drains are best removed by gradually shortening them beginning on the fourth or fifth postoperative day (24).

sis is suggested by recurrent attacks of gastrointestinal bleeding, biliary colic, and jaundice (22). This symptom complex is also present in patients who have hemorrhage into bile ducts as a complication of cholelithiasis, malignant disease of the liver, or hepatic artery aneurysm.

Surgical therapy is desirable in all patients with known or suspected liver trauma (Table 18). Treatment consists of control

Table 18 Surgical Therapy of Liver Wounds

Type of injury	*Surgical treatment*
Sharp incised wounds	Closure by suture
Single bullet hole without fragmentation	Drain Use of packs if spontaneous hemostasis does not occur
Extensive fragmentation	Debridement Drain Pack only if required to control hemorrhage Suture of open wounds
Rents	Debridement Drain Use of tight sutures to control hemorrhage and bile leaks after identifying and ligating *major* vascular and biliary radicals

of hemorrhage and infection, repair of tissue defects, and establishment of drainage (23). It is necessary to control shock, dehydration, and anoxia with whole-blood transfusions, fluid, electrolytes, oxygen, gastric decompression, and analgesics Spontaneous hemostasis occurs in most patients who survive the immediate effects of trauma Parenteral vitamin K is desirable in patients with hypoprothrombinemia. Continued bleeding may result from. (a) direct injury to the vascular tree of the liver, (b) necrosis of liver tissue, (c) infection and sequestration of liver tissue, (d) abnormal coagulation, or (e) hemobilia.

Infection commonly accompanies liver wounds since the liver provides an excellent medium for bacterial growth Infecting organisms may be introduced through an open wound, arise from

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Prognosis in hepatic trauma has improved with better surgical technics and methods for combating shock and controlling infection. The total mortality for wounds of the liver in World War I was 66 per cent and decreased to 27 per cent in World War II (25). Shock, hemorrhage, infections, and renal failure are the most common causes of death. Some patients develop acute hepatic insufficiency and die in coma. Chronic liver disease does not usually result directly from liver trauma but may occur from intercurrent etiologic mechanisms such as nutritional deficiency, viral hepatitis, or biliary obstruction.

RADIATION INJURY

The liver may be injured as a result of therapeutic irradiation or the use of radioactive materials (26). Only minor morphologic changes consisting of central congestion and liver cell atrophy have been noted in atom bomb casualties (27). X-ray therapy to extrahepatic tissues causes biochemical liver dysfunction with abnormal bromsulfalein retention and positive flocculation tests (28). This has been attributed to the systemic effect of radiotherapy and is presumably due to the same basic mechanism that causes alteration of liver function tests after surgical procedures. Biopsy studies of patients receiving total body irradiation demonstrate mild inflammatory reactions, while postmortem material shows degeneration and necrosis of liver cells. Local irradiation of the liver for neoplastic disease is not accompanied by detectable decrease in hepatic reserve; indeed, biochemical tests and morphology often improve (10). Numerous reports have been made on the occurrence of acute liver injury, fibrosis, and malignancy in patients who have received thorium dioxide (Thorotrast) for hepatosplenography (29). Thorium dioxide remains in the reticuloendothelial system and leads to fibrosis and neoplasms. An alpha ray activity, equivalent to that of 1.5–3.0 µg. of radium, is usually given and is the source of radioactivity over a period of years.

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